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BLOOD ALCOHOL LEVELS AND TOXIC DRINKING

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Professor Howard W. Haggard, Head of the Dept. of Applied Physiology at Yale University, has said in effect, "according to dosage alcohol can approximate the therapeutic effects of the various drugs described as sedative, hypnotic, analgesic and narcotic". In this sentence lies the key to the understanding of most excessive drinking.

When alcohol is absorbed, it will appear in the blood and other tissues in proportion to their water content. The effects produced by any given blood alcohol level will vary within a certain range from individual to individual. However, this variation is not great and it is possible to discuss effects from specific levels in general terms. In this paper, blood alcohol levels will be used as a basis for study and will refer to the number of milligrams of alcohol in 100 c.c. of blood. The following interpretation of blood alcohol levels will apply:

(1) The levels below 50 mg. per cent. are encountered in so-called social drinking in which only mild sedative effects are experienced.

(2) Blood alcohol levels in excess of 50 mg. per cent. result in a decrease in tension and inhibitions. Motor control begins to be affected in many people at about the same level.

(3) When 150 mg. per cent. is attained all people are considered to have impairment in motor control and coordination. This becomes particularly significant in driving a motor car and in industrial situations involving the necessity for normal coordination and reaction time.

(4) Blood alcohol levels approximating 200 mg. per cent. are effective in reducing physical pain.

(5) At 300 mg. per cent. most people will be unconscious, but many lose consciousness at lower levels.

(6) Levels of 500 to 700 mg. per cent. are sufficient to depress the respiratory and cardiac centres, resulting in death.

It thus appears that alcohol will appeal to a particular person according to the effect that he desires, and he may acquire dependence upon this particular effect. If a person desires to experience effects produced by the higher alcohol levels, his physiological processes will have to adjust to these levels. It is believed that a breakdown in the ability to maintain metabolic equilibrium during heavy drinking eventually occurs.

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When this breakdown occurs, controlled heavy drinking gradually changes to uncontrolled heavy drinking. Other things being equal, the higher the alcohol levels repeatedly attained, the sooner the breakdown. With this in mind an attempt will be made to discuss some of the reasons for heavy drinking.

The members of the first group, fortunately a small one, are sometimes referred to as the "primary addicts". These people are in such serious conflict with their environment at the time of initial exposure to alcohol that the attainment of a state of unconsciousness through alcohol is grasped at as the only suitable adjustment to painful life experiences. Thus, from their earliest drinking they may force upon themselves sufficient quantities of alcohol to produce levels up to 300 mg. per cent. or even higher, which results in a rapid development of metabolic changes. All members of this group suffer from very serious psychiatric disabilities and even with prolonged psychotherapy have a poor prognosis.

The second group is still more rarely encountered and is only mentioned because it serves to clarify certain points concerning treatment. I refer to the rare individual who has utilized alcohol repeatedly to reduce physical pain. One case has been reported of a stable person who had developed arthritis. When the pain of arthritis began to keep her awake at night, at the suggestion of a friend she took sufficient brandy to counteract the pain. As indicated previously, alcohol levels sufficient to counteract physical pain—the analgesic effect of alcohol—are almost as high as those required to produce unconsciousness. In a surprisingly short time this woman changed from a very moderate drinker, to a controlled heavy drinker, and finally to an uncontrolled addict. She appeared to have acquired an irreversible, abnormal and uncontrollable reaction to alcohol. The first step in her rehabilitation was to make her aware of the need to discontinue this form of medication for life. The rest of treatment involved the proper care of the underlying arthritis.

This principle of treatment holds true regardless of the combination of psychological, social or physical factors which are responsible for heavy drinking and eventual metabolic change. When alcohol addiction has been acquired one must clearly explain the illness to the patient and assist him in finding alternative and more satisfactory ways of dealing with those situations that formerly seemed to demand alcohol.

The third group who eventually become addicted to alcohol initially seek the effects of alcohol levels from 50 to 150 mg. per cent. Their problem is to find a method of reducing tension states. They represent a very diversified group which for study purposes can be broken down into two main classes. The first are those who have a carryover of adjustment problems from childhood into adulthood, but these problems are less severe than with the primary addict mentioned earlier. The real causes of excessive drinking in such cases would be those situations in infancy, childhood and adolescence which had created feelings of resentment and tension.

The second class in this group are those who are involved in adult situations, requiring daily adjustment to a great variety of stresses. Here we find many overworked business executives and professional men who are victims of a stressful life. They have very little

opportunity to do many of the things they might want to do in a 24-hour period and they must have great difficulty in doing as much as is expected of them. Some of these men make valiant but unsuccessful efforts to modify their life habits. When they come home at night they may be unable to relax and enjoy their dinner. Not infrequently the pressure of their work has prevented a normal participation in family activity and affairs. This may lead to added tension and strife at home. With this group particularly, many other aspects of health are affected. Commonly, inadequate diet is maintained, too little time is given for rest, and the capacity to resist all stresses, chemical or otherwise, appears to be reduced.

When studying the alcohol history one may find a prolonged period of moderate drinking prior to the heavy drinking. The heavy drinking, which may be taking place after age forty, may be followed by a surprisingly rapid breakdown into uncontrolled drinking and complete addiction. Even in this group a careful study usually reveals that childhood problems contributed to the difficulties in adult adjustment. However, many of these patients will respond very well to sympathetic treatment by a doctor willing to understand them and explain their problem to them; the insight acquired may lead to a satisfactory abstinent life without need of any institutional care.

There is one group of people who cannot use alcohol to excess regardless of the intensity of emotional strain from which they may be suffering. These are the people who cannot drink, who for a variety of reasons get sick on exposure to even small amounts of alcohol. At the other end of the scale, some people find that from the very start of drinking they can build up much higher alcohol levels than the average with initial impunity. Even after heavy drinking they do not experience hangovers, gastric distress or any of the usual sequelae of overindulgence. When such people drink to excess through ignorance of the "silent" cumulative effect of the higher alcohol levels, they appear to acquire addiction quite rapidly.

In between these two extremes are a great many who increase their tolerance through repeated exposure to alcohol. The increase in tolerance could be considered a significant warning that the intake of alcohol already constitutes a chronic toxic experience which could lead to disease, and could represent the first effort of the body to adjust to this toxic effect.

The last group of alcohol addicts to be discussed are those who have started out as social drinkers. The overworked business executive represents merely one type of person who later deviates from this pattern for specific reasons. Very often the reasons are not obvious. The social pattern of drinking varies greatly from country to country and from community to community within the same country. Drinking to a state of intoxication is a part of the social drinking pattern in most parts of Canada, more noticeable in some areas than in others. This type of drinking is not seen to the same degree in some European countries.

One's first exposure to alcohol is always associated with some aspect of the drinking pattern in a particular community. It has been estimated that two out of three people start drinking through social pressure. This of itself need not be dangerous. From a clinical standpoint, practically all the hazards en-

countered in the social use of alcohol are directly or indirectly due to the intake of sufficient alcohol to interfere with controlled behaviour and/or balanced nutrition. If it is an accepted part of drinking in a particular community to undergo the *acute* toxic experience of getting drunk, this experience might be repeated frequently enough to become a *chronic* toxic experience leading to disease.

One can acquire the habit of chronic toxic drinking as easily as the habit of chronic non-toxic drinking. Disease from alcohol shows no favourites. There appears to be as high an incidence among the professions as among any other group. The medical and nursing professions are exposed to the added hazards of having access to many other chemicals which can ease pain and tension, and lead to still more serious addictions.

Many sayings associated with drinking merely prove our ignorance of what is actually involved. "Holding your liquor like a gentleman" in the fine old military tradition could be interpreted as pre-addictive toxic drinking with an increase in tolerance to alcohol. "One for the road" may have had some significance in the horse and buggy days when the non-anaesthetized brain of the horse could be utilized in finding a way home, but it is utterly stupid in the days of the motor car when the "one for the road" may increase the alcohol level sufficiently to be a hazard in driving. "Bottoms up", "let's kill the bottle", and "you can't fly on one wing" are indicative of an established toxic drinking pattern within our Canadian society.

From a clinical standpoint, the expression "social drinking" should not be applied to drinking patterns which lead to either temporary or permanent disturbance in health. Thus, the 50 mg. per cent. level deserves considerable discussion. It surprises many people to discover the amount of alcohol required to produce a blood alcohol level of 50 mg. per cent. In actual practice most social drinking would routinely involve levels of 20 to 25 mg. per cent., and many people would begin to feel effects at 10. 50 mg. per cent. would be the concentration of alcohol in a 150 lb. person one hour after consuming 3 to 4 oz. of whisky or 2 to 3 pints of beer. This concentration may be maintained by consuming an additional 1 oz. of whisky or 8 oz. of beer every hour after the first hour. For a 4-hour evening of drinking approximately 50 mg. per cent. would be maintained by consuming 7 or 8 oz. of whisky or 5 to 6 pints of beer in this fashion.

Experience has shown that this amount of drinking produces very significant states of intoxication in some people. Whereas a level of 150 mg. per cent. would be sufficient to convict a person of impaired driving ability, certain people would have impaired driving ability at 35 mg. per cent.

It can be demonstrated that a *daily* pattern of drinking of the type described, resulting in a level no higher than 50 mg. per cent. would eventually lead to some impairment in health. Thus, it would be unwise to assume that the quantities mentioned in the example can be absorbed consistently with safety.

In addition to being an anaesthetic alcohol is also an energy food. Both factors, anaesthetic and food, are involved in alcoholic disease. If a person consumed 8 oz. of whisky in an evening, 40% of this, or 3.2 oz. (approx. 90 gm.) would be pure alcohol. At 7 calories per gm. this would provide 630 extra

calories from alcohol alone. In actual practice, about 90% of ingested alcohol is oxidized, the remainder escaping in breath, urine and perspiration. Therefore, if the person maintains an average daily diet of 2,500 calories, his total caloric intake for that day would be in excess of 3,000, of which 20% would be derived from alcohol. Ordinary foods usually contain sufficient vitamin B-1 to maintain the proper balance of vitamin to calories. When the vitamin-calorie ratio drops below a certain point, beri-beri results. In contrast to most foods alcoholic beverages do not contain vitamin B-1 to balance the calories they contain. Beri-beri is one of the commonest "side effects" of heavy drinking; it is more commonly referred to as alcoholic neuritis.

I do not mean to infer that clinical beri-beri would be likely to result from even *daily* ingestion of 8 oz. of whisky, but there might be a mild state of impairment of nutritional balance and a corresponding feeling of gradually impaired well-being. Although the possibility of a relative deficiency of vitamin B-1 has been stressed, corresponding deficiencies with the other vitamins and essential minerals must be similarly considered. In recent years, increasing attention has been paid to sub-clinical, nutritional deficiency states. At the present stage of knowledge, it is impossible to say to what degree a prolonged sub-clinical state of disturbed nutritional balance contributes to the metabolic breakdown in alcohol addiction. However, there is no doubt that in many ways our stupid social drinking practices contribute significantly to alcoholic disease in Canada.

Another effect of persistent moderate drinking is obesity. The fat and carbohydrate sparing action of the heat energy released by alcohol will inevitably result in an increase in weight unless there is a corresponding reduction in caloric intake from non-alcohol sources. If this reduction occurs, the likelihood of still more significant disturbance of the nutritional balance would have to be considered.

Other facts should be kept in mind by any host undertaking to serve alcoholic beverages in an intelligent and safe manner. For instance, a 100 lb. person will have approximately twice as high a blood alcohol level from any given intake of alcohol as a 200 lb. person. The presence of food in the stomach will delay the rate of absorption of alcohol as does diluting of drinks, and it is a much safer social practice to serve alcohol and food together than it is to serve them separately. However, as the protective action of food consumption has its limits, it does not provide a safeguard against heavy drinking. In clinically safe social drinking, the emphasis is on the flavour of a drink and only the *first* mild effects are enjoyed—effects which counteract immediate reactive tensions only. Used in this way, alcohol may enhance appetite, stimulate digestion and become a gracious social custom with recognizable clinical benefits in many instances. The association with people is more important than the fact that alcohol is served. With this in mind it is possible to begin discussing safe drinking intelligently.

Let us assume that a blood alcohol level not exceeding 50 mg. per cent. would be less likely to produce the temporary or permanent impairments in health which are so frequently seen with today's drinking practices. Therefore, the rate of drinking should be adjusted

adequately. Now, if the caloric intake from alcohol did not exceed 10% of the total caloric intake, over any weekly period, the disturbance in nutritional balance should be negligible. By simply keeping an accurate diary concerning drinking for a month any interested person should be able to determine whether or not his drinking remains within this range or has to be modified accordingly. You can make a reasonably accurate estimate of your blood alcohol level by using the following data:

(1) your body weight in ounces,
(2) calculate your alcohol intake in ounces:
   —distilled beverages in Canada—40% alcohol
   —beer—5% alcohol
   —natural wines (non-fortified) 13% alcohol
   —ports and sherries—18.5% alcohol (approx)
   —liqueurs—30% alcohol (approx)
(3) about 1/3 oz. alcohol is metabolized per hour from the time of starting drinking
(4) estimate alcohol percentage of your total weight at any specific time
(5) reduce your answer by 25% (which is an empirical correction factor).

This can be expressed simply by the following formula:

$$A = \frac{W \times L}{75} + \frac{3}{T}$$

Used in this way one could decide in advance what maximum level one would allow oneself on a particular occasion and what pattern of drinking to maintain to stay within this level.

If one wanted to assess blood alcohol level following an unplanned drinking session one would use the following formula:

$$L = \frac{75A - 25T}{W}$$

If one preferred to figure in milligrams per cent. instead of in per cent., and so avoid decimals, as has been done throughout this paper, use:

$$A = \frac{W \times L}{75{,}000} + \frac{T}{3}$$

and

$$L = \frac{1{,}000\ (75A - 25T)}{W}$$

NOTE: This is an attempt to approach the problem of "drinking hygiene" in a quantitative way. We are aware that the points taken into consideration do not cover all conditions involved, but we hope that from this first approach a discussion will arise which will lead to a more complete formula.

It is still more important to take into account the variations in individual response to alcohol. If one is going to drink, it is essential to distinguish toxic from non-toxic drinking. Attention paid to the amount of alcohol oduces an effect, or, in other es one "feel" a drink. When s are experienced at the low to 30 mg. per cent. for ex- one should retain this acute o alcohol and become con-

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ditioned to expect this effect, and accept it as adequate. If it is discovered that a level of 50 mg. per cent. produces little or no effect, drinking should be discontinued for as long as is required for the tolerance to come down to a safer level. After a few months, a trial of drinking might reveal as much effect from 25 mg. per cent. as was formerly experienced at 50.

It is surprising that the "hangover" is so lightly regarded. If people would ingest any other chemical in such quantities as to produce illness the following morning, they would be genuinely and justifiably alarmed. There is no reason to adopt a different attitude towards alcohol than towards any other chemical. Even the *mildest* "hangover" is proof that the preceding exposure to alcohol has been a toxic experience. A pattern of drinking that produces hangovers should be modified so as not to produce them. We have no way of knowing how frequently we can go through such toxic experiences before significant metabolic changes are brought about. When we eventually fail to have hangovers from the amounts of alcohol that initially produced them, it merely means that a still more significant state of *chronic* toxic drinking has been reached in which normal metabolism has already been altered.

Non-toxic drinking should not result in any type of hangover. Whenever amounts of alcohol are taken that produce hangovers, these acute toxic experiences must be spaced far enough apart to allow complete recovery and thus avoid having them become cumulative in effect, resulting in increased tolerance and eventual disease. If a person suspects that on a particular occasion he is liable to drink enough to have an acute toxic effect with hangover, he should at the very least recognize his responsibility to others and not drive a motor car. Should he find that a pattern of moderate drinking does not do enough for him, he obviously needs some other kind of assistance than that of repeating the anaesthetic effect of high alcohol levels. His compulsion to experience anaesthesia is a symptom of an underlying pathological condition which should be investigated by the physician or the psychologist.

SUMMARY: Alcohol is man's oldest anaesthetic. As with any other chemical, one can acquire disease from repeated over-exposure to alcohol. In alcohol addiction we deal with two disorders—the factors responsible for repeated heavy drinking to the point of disease, and the superadded disease from alcohol itself. Thus, a vicious circle is established. If we are to prevent disease from alcohol, we must do something entirely new and constructive concerning the social, psychological and physical factors which at present are responsible for chronic toxic exposure to alcohol to the point of disease. It is considered that to date ignorance, carelessness, and unhygienic drinking habits are responsible for more disease from alcohol than severe instability.

For anyone who indulges repeatedly in heavy drinking, there is no known way to escape pathological changes. For this reason, it should also be mentioned that it is not necessary for anyone to drink at all, and unless one knows what one is doing, the hazards from drinking may far outweigh the benefits.

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This can be expressed simply by the following formula:

$$A = \frac{W \times L}{75} + \frac{3}{T}$$

A = alcohol intake in ounces.
L = level of alcohol in body—expressed as percentage of body weight.
W = body weight in ounces.
T = time from onset of drinking in hours.

Used in this way one could decide in advance what maximum level one would allow oneself on a particular occasion and what pattern of drinking to maintain to stay within this level.

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It is still more important to take into account the variations in individual response to alcohol. If one is going to drink, it is essential to distinguish toxic from non-toxic drinking. Attention should be paid to the amount of alcohol that *first* produces an effect, or, in other words, makes one "feel" a drink. When these effects are experienced at the low levels of 10 to 30 mg. per cent. for example, then one should retain this acute sensitivity to alcohol and become con-

ditioned to expect this effect, and accept it as adequate. If it is discovered that a level of 50 mg. per cent. produces little or no effect, drinking should be discontinued for as long as is required for the tolerance to come down to a safer level. After a few months, a trial of drinking might reveal as much effect from 25 mg. per cent. as was formerly experienced at 50.

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THE RENAL CONTROL OF SALT AND WATER†

A. RAPOPORT M.D., M.A.*

Introduction

That the internal environment of the body is maintained constant and that this constancy is largely a result of the activity of the kidney is by now a text-book truism. As Smith (1) has phrased it "in the last analysis, composition of the plasma is determined not by what the body ingests but by what the kidneys retain and what they excrete".

However, not all the elements of the internal environment are controlled equally by the kidney. For instance, substances such as urea, which is formed in the liver, glucose which is stored as glycogen in the liver and muscle, and calcium which is stored in the bone—all these substances have organs other than the kidney vitally concerned with their regulation. For these elements, the kidney functions as a safety valve, excreting any excess over their desirable levels in the body fluids. In the case of electrolytes such as sodium, chloride and potassium the situation is quite different. For these there are no organs of storage; for these the kidneys are the all-important organs of regulation. A qualification may be interjected here; the distribution of these electrolytes in the various fluid compartments of the body can be influenced by a number of hormones but the question of their retention and excretion rests ultimately with the kidney.

It should be recognised, at this point, that in discussing renal control, the use of the term "salt" is misleading since the kidney does not necessarily handle sodium and chloride in the same fashion. What follows in this presentation will deal mainly with the renal control of sodium. At the same time, it is impossible to discuss the renal regulation of sodium without mentioning its control of water. However, there are differences in the kidney's treatment of these two substances and these will be pointed out in the presentation.

The renal control of electrolytes and water is an extremely controversial problem, abounding in theories. This is to be expected because of the great difficulty in performing *direct* experiments on the kidney whose constituent units, the nephrons, are microscopic in size. The innumerable indirect experiments which have been devised yield data capable of several interpretations; hence the controversies.

The Concept of the "Smith School"

This paper will be restricted to an examination in detail of the theory advanced by Homer Smith and his associates in New York (1, 2, 3). His concept has been most widely adopted, appears to correlate best the various experimental data of many investigators and has been applied clinically to a number of electrolyte problems, notably by the proponents of the "forward failure" theory of heart disease.

For the sake of clarity an outline of the theory, in its simplest form, will first

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†From a seminar presented before the Department of Pathological Chemistry, University of Toronto, 1952.

be presented. This will then be followed by an analysis of the important postulates and experimental data upon which the theory is based.

The nephron or functioning renal unit is depicted schematically in Fig. 1 and is seen to be composed of a glomerulus, proximal tubule, thin segment and distal system made up of distal tubule and collecting duct. As the plasma is filtered in the glomerulus, the filtrate has the same concentration of electrolyte and non-protein solutes as the plasma and is therefore isotonic with it. During the passage of the fluid through the proximal tubule about 7/8 of the sodium is reabsorbed actively, that is by a process involving energy expenditure on the part of the cell. Consequent upon this reabsorption, the fluid in the proximal tubule is rendered hypotonic to the renal interstitial fluid and as a result of this osmotic imbalance, water is reabsorbed *passively*. However, the reabsorption of water does not quite match that of the sodium and other solutes so that the fluid leaving the proximal tubule is slightly hypotonic. In the thin segment osmotic equilibration occurs with further passive diffusion of water so that the fluid emerging is isotonic with plasma.

Because the water reabsorption in the proximal tubule and thin segment occurs passively as a result of solute reabsorption it has been designated "*obligatory water reabsorption*". Proximal reabsorption appears to function as a "bulk transfer mechanism", serving to reduce the gross volume of the glomerular filtrate as well as the absolute amount of its constituents such as electrolytes, glucose, urea, etc.

In the distal system fine adjustments are carried out on smaller volumes of fluid. The reabsorption, in this segment, of both sodium and water is viewed as being *active*, requiring expenditure of

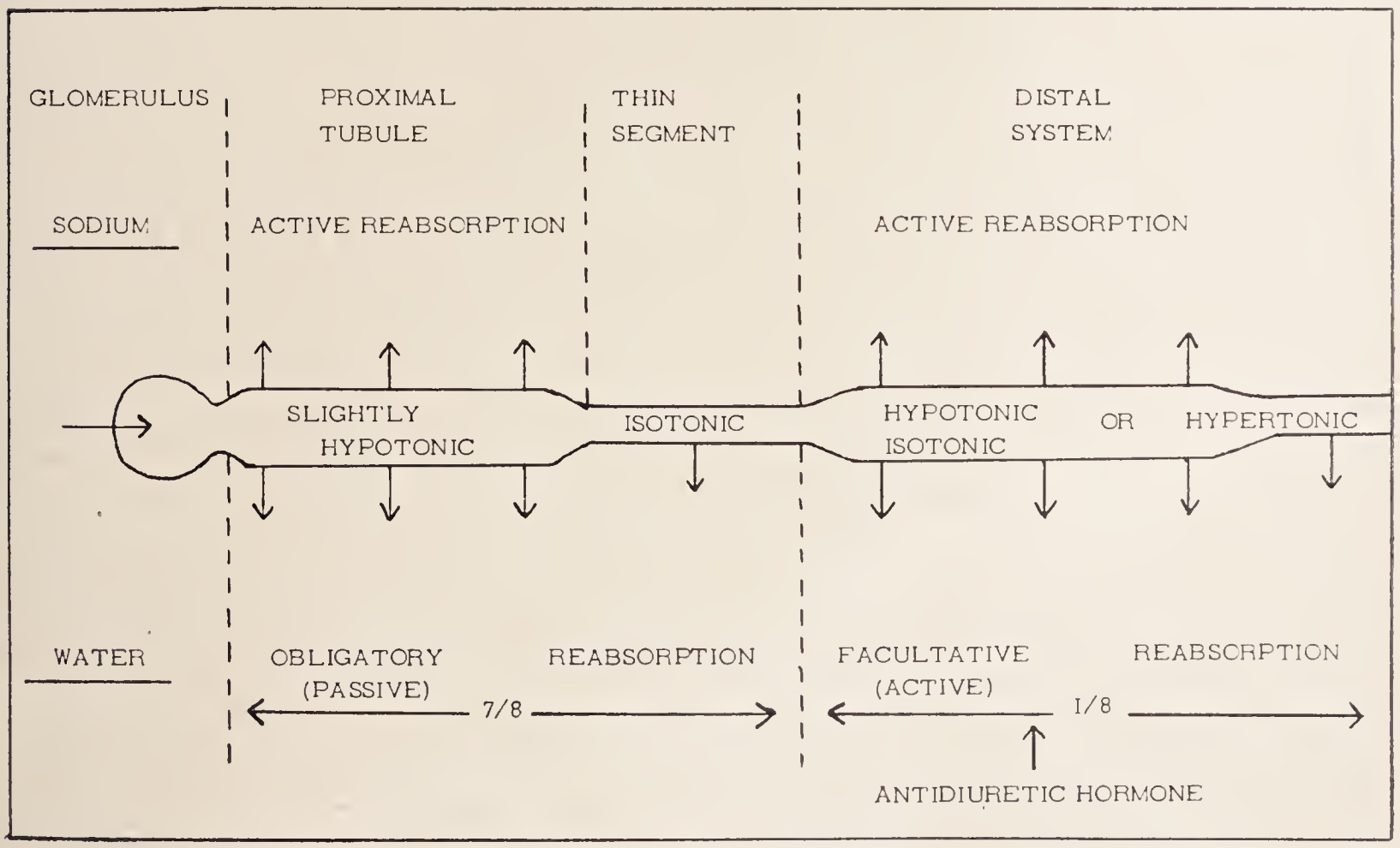

FIGURE 1

energy, and to a certain extent each is independent of the other. The reabsorption in the distal segment of water is designated *facultative* because it is conditioned by the body's need for water and is responsive to physiological stimuli. This reabsorption is believed to be mediated by the antidiuretic hormone of the pituitary gland. If solute reabsorption continues normally in the event of a depressed secretion of this hormone such as occurs following the ingestion of large volumes of water (water diuresis), then the final urine will be hypotonic. If the solute and water reabsorption are balanced then the urine will be isotonic. And if there is increased secretion of antidiuretic hormone as in dehydration, then there will be increased water reabsorption beyond that of the solutes and the final urine will be hypertonic.

The reabsorption of sodium in the distal system is regarded by Smith as being conditioned by the absolute quantity emerging from the proximal system per unit time. If this quantity of sodium is less than the maximum amount which the tubule can reabsorb then very little of the ion will be excreted; if it is more, then sodium will be excreted.

Thus, in summary, Smith views the proximal system as removing a more or less fixed proportion of sodium and water from the glomerular filtrate whereas further treatment of the sodium by the distal tubule is dependent upon the absolute quantity of the ion delivered to it per unit time. The magnitude of this quantity will depend, in turn, upon the size of the load of sodium delivered to the proximal system from the glomeruli. The sodium load is a combination of two factors, the glomerular filtration rate (G.F.R.) or volume of filtrate per unit time and the concentration of sodium in the filtrate. If the load is increased due to a rise in the plasma sodium and/or a rise in G.F.R. and a fairly fixed proportion is removed in the proximal system there remains a greater quantity to be presented to the distal system. The converse holds true as well. Reduction of the sodium load leaving the glomeruli will lead to a smaller quantity being presented to the distal system and if this is below the maximal reabsorption capacity of the latter then very little will be excreted in the urine.

To illustrate the system as a whole, suppose the G.F.R. to be increased. The distal load of sodium will then be increased and may come to exceed the distal reabsorption capacity, leading to the excretion of the excess sodium. When the excretion of sodium is thus accelerated the sodium content of the plasma will decrease and the consequent reduction of osmotic pressure acting through the supraopticohypophyseal system will lead, it is believed, to a diminished production of antidiuretic hormone and a decreased distal reabsorption of water until the critical osmotic pressure of the plasma is restored. Conversely if the G.F.R. is reduced, the distal load of sodium will fall below the maximal reabsorption capacity and sodium reabsorption will be essentially complete. Where sodium reabsorption exceeds water reabsorption, the ultimate increase in the osmotic pressure of the plasma, operating through the supraopticohypophyseal system, will increase the distal reabsorption of water until, once again, the critical osmotic pressure of the plasma is restored.

By combining the renal mechanism controlling the excretion of sodium, the supraopticohypophyseal mechanism for controlling the excretion of water and the glomerular apparatus controlling the

filtration rate, an integrated system is envisaged that will not only regulate the osmotic pressure of the extracellular fluid, but its volume as well.

Having thus outlined, in somewhat oversimplified fashion, Smith's concept of the renal control of sodium and water an examination will now be made of the evidence upon which the concept is based.

Evidence for the Concept of the "Smith School".

1. *The Division of Tubular Reabsorption of Water into Two Phases: Obligatory and Facultative.*

Patients with diabetes insipidus and dogs in whom this condition has been experimentally produced both lack antidiuretic hormone and continually excrete large volumes of dilute, hypotonic urine. Yet this volume of urine never exceeds 10–20% of the volume of fluid passing the glomerular filter.

Normal humans who are "loaded" with water and made thus to undergo what is termed a "Water diuresis" (in a sense, a physiological diabetes insipidus —since antidiuretic hormone is suppressed) excrete large volumes of urine which once again do not exceed 10–20% of the fluid passing through the glomeruli. Thus by suppressing antidiuretic hormone either pathologically or physiologically one appears to affect only one phase of water reabsorption amounting to 10–20% of all that is filtered through the glomeruli. This suggests another phase, 80 to 90% of which is unaffected by antidiuretic hormone.

Perhaps the most convincing evidence of the two-phase reabsorption of water by the renal tubules lies in the experiments performed on dogs by Shannon (4). These related urea reabsorption to the rate of urine flow through the entire range of the latter. (See Fig. 2) The creatinine U/P ratio (U = concentration in urine, P = in plasma) is a convenient way of measuring water absorption or excretion by the tubules. In the glomerular filtrate before any water reabsorption has occurred, this ratio will equal one. Since creatinine is neither reabsorbed nor excreted by the tubules, the increase in U which occurs as the fluid passes down the tubule must be due solely to reabsorption of water, and thus a U/P ratio of 8 means that 7/8 of the fluid that was filtered has been reabsorbed or, alternatively, that 1/8 of it has been excreted. (Charting the ratio on a logarithmic scale is a convenience permitting a greater range, here 2 to 600, to be included in the graph.) The ratio of urea clearance to creatinine clearance reflects the fraction of filtered urea that is excreted. The higher the ratio, the more of the filtered urea that is rejected by the tubules or the less that is reabsorbed by them. The converse holds true as well.

The open circles (curve B of Fig. 2) represent observations made throughout the *entire normal* range of urine flow, that is between the extremes of water deprivation and water diuresis. During water deprivation the creatinine U/P ratio reached its maximal value of 600 or more, when 599/600 of the water of the glomerular filtrate had been reabsorbed. During water diuresis, the lowest creatinine U/P ratio reached in these dogs was about 15 when 14/15 of the water had been reabsorbed—(actually a U/P ratio of 8 is more nearly representative in both dog and man during maximal water diuresis (1)). The solid circles (curve A) represent observations made during the *abnormal* forced osmotic diuresis induced by the intravenous in-

fusion of substances such as glucose and sodium sulphate. Here the osmotic pressure of the infused solute retards water reabsorption in the tubule and makes it possible to reduce the creatinine U/P ratio to about 2.0, where only 50% of the water of the glomerular filtrate is reabsorbed. It will be seen that at higher urine flows (lower creatinine U/P ratios), less urea is reabsorbed by the tubules and that the data divide themselves into two rectilinear phases, A and B. The difference in slope of the two curves suggests that two processes are involved in the reabsorption of urea. The one represented by the curve A is operative at creatinine U/P ratios from about 1.0 to 10, that is in the phase during which 0–90% of the water is reabsorbed. Phase B is operative in the final 10% of water reabsorption.

Restated, Phase A of urea reabsorption

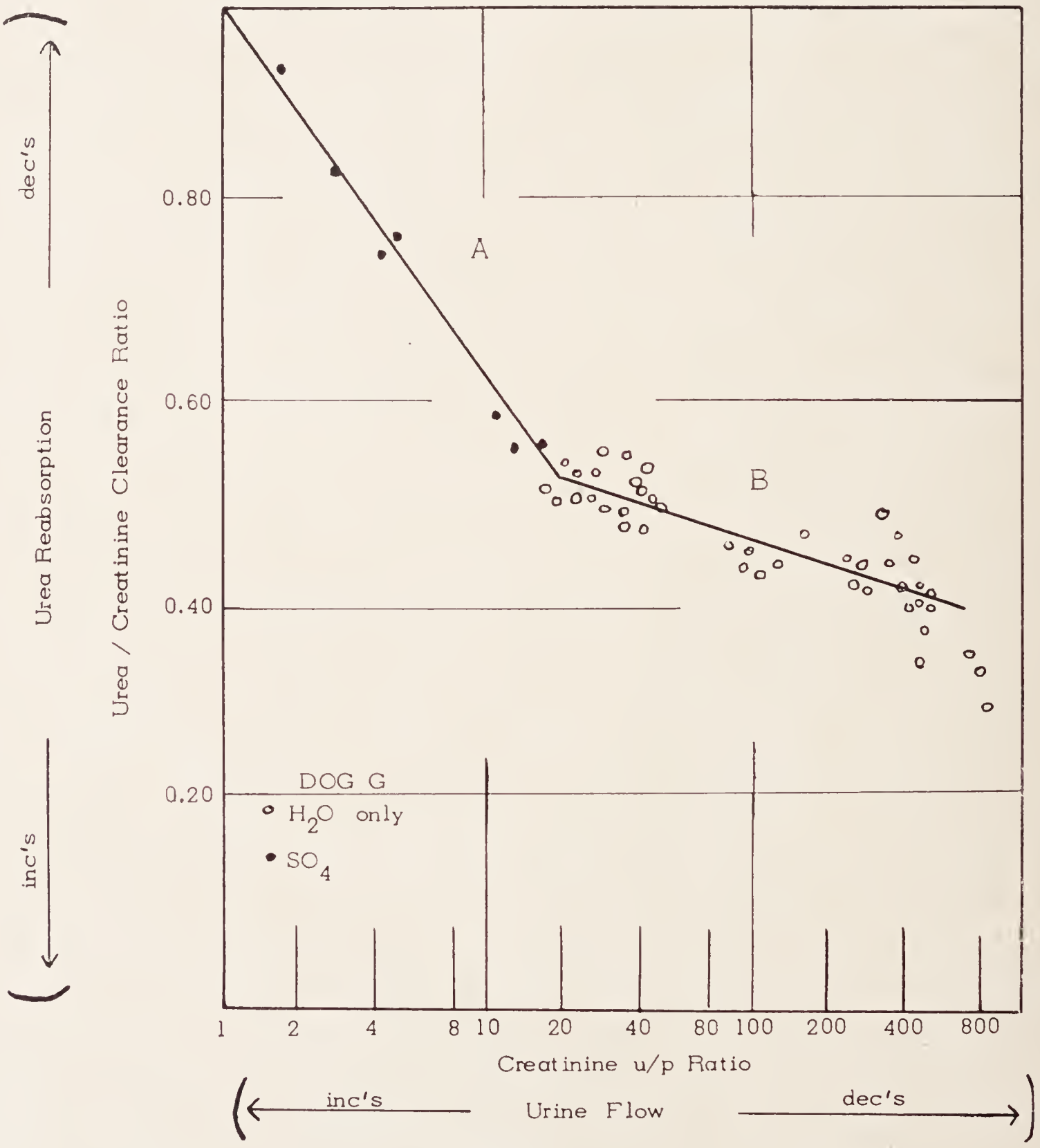

FIGURE 2

occurs in that portion of water reabsorption during which 80 to 90% of filtrate water is reabsorbed. This portion which is unresponsive to physiological stimuli and occurs regardless of the body's state of hydration, is hence termed *obligatory*. Phase B of urea reabsorption occurs during the reabsorption of the remaining 10–20% of filtrate water which is influenced by physiological means (hydration, dehydration, etc.) and is termed therefore *facultative*.

Incidentally, the fact that line A extrapolates to a urea/creatinine clearance of 1.0 when the creatinine U/P ratio is 1.0 means that there is no reabsorption of urea unless there is reabsorption of water or in other words, that the reabsorption of urea is passive.

2. *Function of Proximal Tubule*

The next logical step in this theory is the localization of these two phases of water reabsorption, the obligatory 85%, and the facultative 15% (average figures). The evidence upon which this is based stems from the experiments of Walker, Oliver, Bott and MacDowell (5, 6) who applied the micropuncture technique developed by Wearn and Richards in amphibians to living mammalian kidneys. Since these are the only experiments relating to renal control of sodium and water in mammals which yield *direct* information and since they are quoted by all workers in this field, let us examine them in some detail.

The work was done largely on guinea pigs and rats. One kidney was removed prior to the experiment to cause hypertrophy of the other. In the guinea pig, under anaesthesia, the gastrointestinal tract was removed and the abdominal cavity was filled with liquid petrolatum so that the kidney was covered to a depth of 5 mm. The oil prevented the kidney from drying, aided in the diffusion of light and could readily be distinguished from the watery fluid that arose in the nephrons. The vast majority of tubule segments appearing on the kidney surface proved to be portions of proximal convolutions. Urine flow was increased by the use of intravenous saline or sucrose infusions. With the micropipette inside the tubule lumen, a short column of red oil was injected. This passed distally and then was held immobile, thus assuring a better collection of fluid and preventing contamination from fluid distal to the oil droplet. Following the experiment, the kidney was macerated in acid and the nephrons identified and dissected under a microscope. The lengths of various portions of the nephron were measured. Chemical analyses were made with ultramicro methods on the minute volumes of 0.03 to 0.70 cu. mm. collected in the micropipette. Osmotic pressure of the fluid at various levels were determined by vapor pressure comparisons with plasma. With this technique, the experimenters were only able to reach half way down the proximal tubule. At this point the creatinine U/P ratio was 2.5 and by extrapolation the authors calculated that by the end of the proximal tubule this ratio would reach 5.0, which would mean that 4/5 or 80% of the glomerular filtrate had been reabsorbed. Furthermore the tubular fluid was isosmotic with the plasma and if this were true to the end of the proximal tubule then it follows that as much sodium had been reabsorbed as water.

It is thus a natural step to locate the obligatory reabsorption of an average of 85% of the filtrate water in the proximal segment. The facultative reabsorption of the remaining 15% would then take place in the distal system. Similarly 85%

of the filtered sodium must be reabsorbed proximally and the remaining 15% handled in the distal segment.

As regards the nature of proximal reabsorption one further experiment should be mentioned. Wesson and Anslow (7) have shown in the dog, that, during osmotic diuresis induced by the intravenous infusion of hypertonic mannitol solutions, as much as 65% of the water of the glomerular filtrate may be excreted in the urine at a time when only 13 to 27% of the filtered sodium is excreted. Under the conditions of these experiments, the flow of urine is so great that any changes in composition of the urine effected by the distal tubule are relatively minor in magnitude, and the composition of the bladder urine can be taken to represent the composition of the tubular urine at the end of the thin limb. The fact that much less sodium is swept out by the osmotic diuresis shows, first, that the reabsorption of sodium in the proximal tubule is operationally independent of the reabsorption of water and second, that sodium reabsorption is an active process rather than a process involving passive diffusion of sodium along with whatever water is reabsorbed. Since the osmotic pressure of the urine closely approaches that of the plasma during osmotic diuresis, the authors concluded that the proximal reabsorbate is in the net isosmotic with the plasma. The simplest explanation is that, as sodium and other constituents of the proximal tubular urine are reabsorbed, water diffuses back from the proximal tubule or thin limb to maintain an osmotic U/P ratio close to 1:0.

3. *The Function of the Thin Segment*

Because the thin segment occurs only in the two Classes, birds and mammals where antidiuretic hormone promotes water reabsorption (1), it has been felt by some that this segment is the locus of formation of a concentrated urine and of osmotic work. This has never had strong appeal because the low epithelium of the limb does not, by contrast with the cuboidal cells of the distal tubule, seem cytologically constituted for such a function. Perhaps the strongest argument against the formation of hypertonic urine in the thin segment is the fact that protein casts are never found in this segment. Casts first form in the ascending limb of the distal tubule, with increasing precipitation in the distal convoluted tubules and collecting ducts. Insofar as cast formation is related to increasing concentration of protein, this circumstance indicates further water reabsorption in the distal system, which could scarcely be possible if the urine in the thin segment were already hypertonic to the plasma. The present interpretation would be that the thin limb serves to promote osmotic equilibration, by passive diffusion of water, between tubular urine and plasma after the bulk of the sodium and other solutes has been reabsorbed proximally. In other words, if the fluid leaving the proximal tubule is hypotonic to plasma, in the thin segment water alone diffuses out rendering the fluid isotonic to plasma.

4. *The Function of the Distal System*

As we have observed, it is this segment of the nephron that is of supreme importance in the renal regulation of sodium and water. While on the average only about ⅛ of the sodium and water that have been filtered remain to be treated by the distal system, yet, normally no more than this proportion of filtered sodium and water is ever ex-

creted in the final urine. The reabsorption, of the distal system, of both sodium and water is considered active as evidenced in the case of sodium by the ability to remove all but a trace of this ion from the urine and, in the case of water, by the ability to elaborate a markedly hypertonic urine in the face of an opposing osmotic gradient.

As regards water control, we have discussed how facultative reabsorption has been localized in the distal system. Since this type of reabsorption appears to be exercised by the antidiuretic hormone, the site of the action of the latter has likewise been placed in the distal system. The stimulus for the release of the antidiuretic hormone appears to be a changing osmotic pressure of the plasma but many points remain to be settled in connection with this thesis.

The situation in the case of distal reabsorption of sodium is much more indefinite. In fact, it is probobly no exaggeration to state that the identification of the precise stimulus or stimuli regulating the tubular reabsorption of sodium is the most consequential problem in renal physiology today. Clinically, increased tubular reabsorption of sodium has been incriminated causally in a variety of edematous states including congestive heart failure, cirrhosis with ascites and toxemia of pregnancy.

Smith has postulated that the distal reabsorption of both sodium and water is governed by a Tm value or maximal reabsorption capacity. In his view, the most important consideration is the load of filtrate presented to the tubules. The load, in review, is made up of rate of flow of fluid and sodium concentration in it. If the load presented to the distal segment exceeds their respective Tm's then excretion of both sodium and water occurs. Conversely, if the load falls below the Tm then minimal excretion takes place.

Critical Evaluation of the "Smith Concept" of the Renal Control of Salt and Water

This concept represents an admirable attempt to integrate into a unified scheme the complex experimental data in this field. However, it has been accepted as fact by numerous investigators who have in turn based their interpretations of new experiments upon it.

Perhaps, therefore, a brief critical assessment of the evidence for the concept is warranted. One is willing to accept that the reabsorption of water occurs in at least two phases but the localization of these phases must still be regarded as highly tentative. The crucial experiments of Walker et al. (5, 6) were, after all, highly unphysiological, performed as they were in uninephrectomized animals, under anaesthesia and under the influence of osmotic diuretics. Furthermore in the interpretation of their data extrapolations were made and to some extent negative results were neglected. This work is badly in need of confirmation and extension.

The contention that the thin segment is incapable of osmotic work is highly debatable. The flat epithelium is no objection because as Smith himself recognizes (1) the similar epithelium of the fish gill has been shown to do osmotic work. Furthermore one is intrigued by the observation that only in those two Classes possessing a thin segment can antidiuretic hormone promote water reabsorption. This may well prove to be more than coincidence.

Undoubtedly the greatest amount of criticism of this theory of the New York School has been directed against the Tm or limited reabsorption of sodium

and water in the distal tubule. There is next to no experimental data supporting such a view and, indeed, hardly anyone has been able to devise an experiment to test purely distal reabsorption. On the other hand, Black et al (8) have shown that under proper conditions the ceiling on sodium reabsorption can be markedly raised and the tubules be made to reabsorb quantities of sodium greatly in excess of the usual physiological demands.

Furthermore Smith's belief that the sodium load delivered to the tubules is the chief factor determining renal retention and excretion of sodium has been warmly disputed. A host of investigators have reported results which indicate that active alterations in tubular reabsorption of sodium are more important in regulating excretion of this ion than are changes in glomerular filtration rate. Only a few of these references will be listed here; the interested reader may consult their bibliographies for further details. (9, 10, 11, 12).

Probably the greatest aid in reconciling Smith's theory with these conflicting experiments would be to designate the distal tubular reabsorption of sodium as *facultative*, similar to that of water. This would mean that the distal tubule reabsorbs sodium in response to the body's need to retain or dispose of the ion with no ceiling attached to this activity. It would imply as well that physiological stimuli arising systemically confer upon the tubules precedence over the glomeruli in the renal regulation of sodium. Thus there would be introduced into the scheme, in addition to antidiuretic hormone, those hormones influencing the kidney's reabsorption and excretion of sodium. These include secretions of the adrenal, pituitary and possibly thyroid glands as well as perhaps yet unidentified hormones.

In Fig. 3 is depicted the relationship between the kidney's regulation of sodium and water and the systemic characteristics to which this regulation must be attuned. Thus alterations in the osmotic pressure, the volume or the pattern of the extracellular fluid may influence the excretion of sodium and water by changing the load presented to the tubules and/or by changing the distal system's reabsorption of these constituents. Changes in the latter are likely exerted, in part at least, by the hormones previously mentioned. Limitations in space preclude a more intensive con-

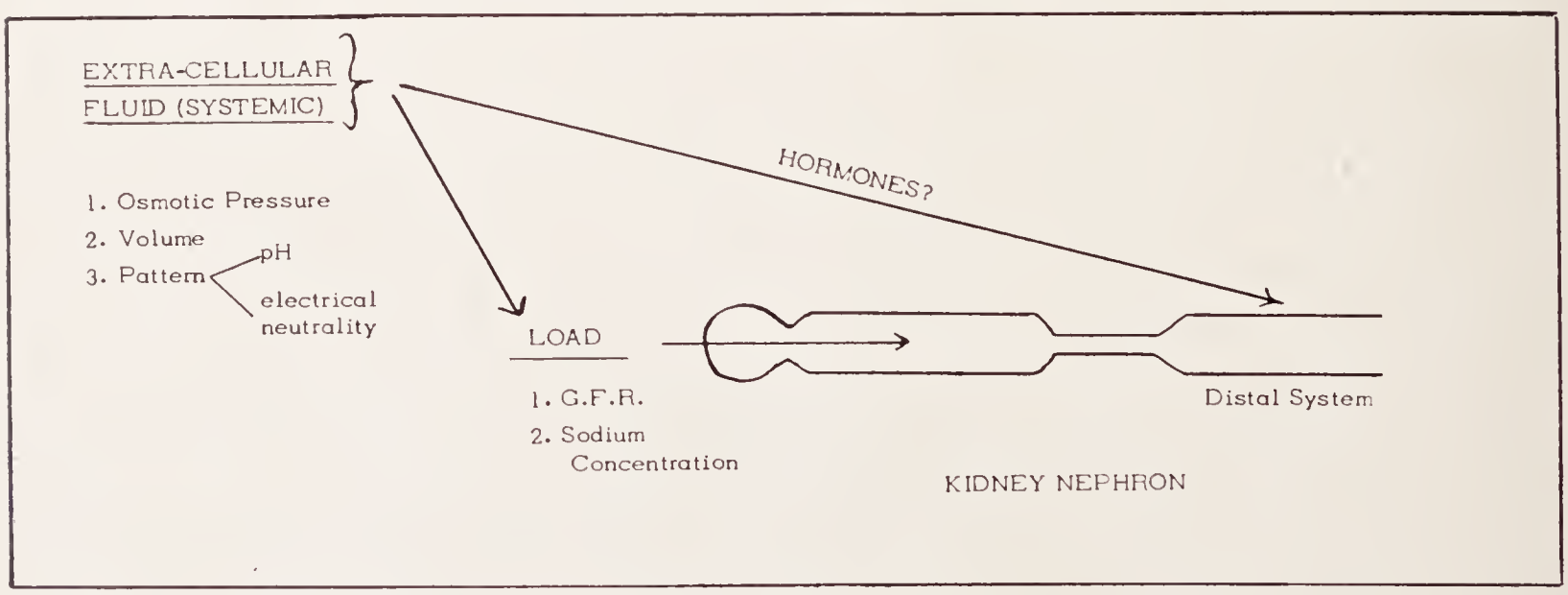

FIGURE 3

sideration of the action of these hormones but their importance may be decisive.

Summary and Conclusions

The major portion of this paper has concerned itself with an examination and critical evaluation of the concept advanced by Homer Smith and his school regarding the renal regulation of sodium and water. It is recognised, of course, that this concept is based on the experiments of numerous investigators, not necessarily of the Smith school but that the latter has been foremost in integrating the various experimental results into the scheme herein presented.

It is observed that many investigators, contrary to Smith, consider the renal tubules more important than glomerular filtration in controlling sodium excretion. Furthermore it is felt that Smith's concept does not consider adequately the role of systemic influences in regulating sodium excretion. A *facultative* reabsorption of sodium in the distal tubules which is attuned to these influences, is suggested. Hormones are considered the likely agents whereby systemic influences control this reabsorption.

Finally, it is to be regretted that so much of what constitutes Smith's *concept* has come to be regarded in the literature as *fact*.

An examination of the basic experiments upon which the theory is based reveals that many of the details are yet unproven and that some are entirely speculative. It will take more *direct* experiments, perhaps along micropuncture lines, to settle and clarify the numerous debatable issues in this field.

Acknowledgement

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SIR JOHN ROLPH—FORGOTTEN PIONEER

F. McCONNELL, M.D.*

Two years ago while reading for an article on the history of the University of Toronto Medical School, I was repeatedly confronted with the figure of a Dr. John Rolph. Once acquainted, one cannot help but pursue him further, and there emerges a most interesting person. Now, I hope that I may be able to cast some well deserved light on the man, and inevitably also on the origins of our University of Toronto Medical School.

As you enter the building of the Academy of Medicine in Toronto, if you turn to your left you will see a full-sized portrait of a man. He is a stocky ruddy, clean-shaven, rather belligerent looking person, and below on the brass tablet you will read:

> "The Hon. John Rolph M.D. M.R.C.S. L.L.D. 1793–1870
> Represented Counties of Middlesex 1824 and Norfolk 1835, Minister of Crown Lands in the Hincks Govt. of 1851–54
> Father of Medical Education in Upper Canada."

This is a modest enough tribute to the man who, to quote the historian Dent, was "unquestionably one of the ablest men who has figured in political and professional life in this country".

England was the birthplace of Rolph; he was born just as Napoleon was commencing his wars of conquest. His physician father emigrated to the colony of Canada in 1810, and young John soon followed. The rugged unharnessed country must have been a challenge to this youth for he was to return to England only for the few years it took him to gather his professional training. He went first to Cambridge where he was recognized as having a remarkable intellect even for that remarkable place. He underlined this fact by studying both Medicine and Law, probably concurrently. In Law he was called to the Bar from the Inner Temple. In Medicine, after studying under Sir Astley Cooper, and at St. Barts. and Guy's Hospitals, he graduated and soon after took his membership in the Royal College of Surgeons.

He was now equipped to set out on his arduous course. He returned to Canada in 1821, to a district near London, and began the practice of Law. He was one of the first lawyers in Upper Canada, and a very successful lawyer he was, later stated to be "the most eloquent man at the Upper Canada Bar." His eloquence he also used in various political movements and he was in due course elected to the Legislative Assembly of Upper Canada.

The colony of Upper Canada, a fringe of growing pioneer communities gathered chiefly around the head of Lake Ontario, was ruled by a Crown appointed governor sent out from England. Around this ruler gathered a favoured few, the wealthy merchants, the Anglican clergy, and others. At their disposal was such patronage as the appointment of judges and the distribution

*From a paper delivered to the Osler Society.

of Crown lands. All these privileges were abused, but the most irksome was the matter of the "Clergy Reserves". This, in effect was the wholesale allocation of Crown Lands to the state supported Church of England. To the poor struggling colony the loss of the revenue which would otherwise have come from the sale of these great tracts of land was to become a desperate matter.

To placate the growing demand by the growing number of English and Loyalist settlers for responsible government, a representative but powerless Legislative Assembly had been set up. It was here that the Reform Party struggled against the autocracy. Here Rolph's voice was raised in appeals for responsible government, for habeas corpus, and for abolishment of the Clergy Reserves. Here William Lyon MacKenzie loudly led the Reformers, so savagely attacking the Government that he was repeatedly evicted from the House.

Rolph, a professional man of high standing, showed his usual courage and independence of spirit by allying himself with the Reform party, and soon his keen mind and "silver tongue" won him a leading place in the Reform group. His speech attacking the Clergy Reserves became the party text on the subject for many years. It can be read with pleasure and profit today, so beautifully does it delineate the proper spheres of Church and State.

Nevertheless, Rolph remained active in Medicine, and one fellow lawyer writes of him; "My first introduction to Dr. John Rolph was at the assizes in London in about the year 1827 when he came into the court carrying a pair of saddlebags in his arms, one side filled with surgical instruments, vials, and packages of medicine, the other with briefs and legal documents and books. He would attend to a case in court, and when through catch up his saddle bags, mount his horse tethered nearby and ride off to visit a patient. He was an eloquent counsel".

He must have been a good doctor as well, to judge by an advertisement appearing at this time:

> "Mr. John Rolph intends here to observe the rule of confining his attendance to those families which shall employ him by the year upon the terms usual in the profession, and who shall acquaint him early with their wishes before they are urged by existing sickness."

In 1828 Rolph, dissatisfied with a court judgement, renounced his practice of law by flinging off his cloak and stalking out of the court. Medicine now was his sole profession and he rapidly became as eminent in that field as he had been in Law.

In 1831 he moved his practice to the capital of Upper Canada—York. A contemporary author remarks about our fair city. "It stands on a piece of marshy ground and is better calculated for a frog pond or a beaver meadow than for the residence of human beings. Those who selected the site may have had a fondness for the roaring of frogs but could certainly have had no very great regard for preserving the lives of His Majesty's subjects."

It is difficult to imagine the difficulties encountered in the practice of medicine at this time. Waves of ill-provided immigrants were coming to Upper Canada, and overcrowding with resulting filth and disease was the accepted lot of all but the wealthy. The nature of common

diseases was unknown. "Inflammation of the Lung" (tuberculosis) was thought to be an inherited ailment the course of which was inevitably fatal. Diphtheria was the scourge of children as rows of headstones in old churchyards demonstrate. Typhoid and typhus were endemic. Public Hygiene was unknown. Toronto is described as late as 1854: "Herds of gaunt swine grunting through the leading avenues of the city, and piles of garbage which east, west, north, and south horrify the smell of the wretches who drag on an existence in that pestilence engendering clearing". Droves of quacks peddled all forms of herbs, amulets, and incantations to the disease wracked people.

Against all this a small band of doctors mustered their armamentarium of bleeding, blistering, opium, calomel and some surgery. Popular prejudice opposed the use of smallpox vaccine. Conditions of practice were hard, and it was a long distance to the medical schools of McGill or the United States.

The shortage of properly trained physicians prompted a general demand for Rolph to train young men in the profession. This was Rolph's true field for he was an excellent teacher and his few followers soon expanded into a small school. It is interesting to learn that the Lieutenant Governor at that time (1832) urged Rolph to start a medical school for the newly opened King's College, but he refused. Fifty years later the descendant of Rolph's private school was to become the Faculty of Medicine of our University—the descendant of King's College.

But for a period Rolph's political work was to dominate his life. He was the most popular political figure in the country, and the townspeople of York actually petitioned that he have his portrait painted at public cost. He was the accepted and respected leader of the Reform Party. William Lyon MacKenzie was the prophet of the party, the firebrand. The boundless energy with which this man campaigned up and down the land was largely countered by his violent and irresponsible outbursts. His savage attacks on the Colonial Government were accompanied now by the almost open organizing of armed rebellion throughout the rural areas.

For years urgent pleas for a minimum of reform had been spurned by the Government. The time was undoubtedly ripe for an armed protest. Unfortunately the man who so vigorously acted as midwife to rebellion, was by incompetence and irresponsibility, to destroy his own laboriously built work.

At this time Toronto was incorporated as a city, and Rolph, as a gesture of political sympathy for MacKenzie, declined the first Mayorship, in favour of MacKenzie.

In November of 1837, MacKenzie rode into Toronto to advise Rolph and other Toronto reformers, that the forces of rebellion were prepared to march. Toronto was to be seized, and the corrupt colonial Government of Sir Francis Bond Head was to be replaced by a government with Dr. John Rolph at its head. Rolph well knew of the irresponsible nature of MacKenzie but he also knew of the great popular yearning for democratic government, and MacKenzie apparently had very large forces at his disposal. Also, the government had only a token force at its command, and was too inefficient to raise a much larger one. It was agreed that MacKenzie would lead the rebels into Toronto on December seventh.

A large number of crudely armed farmers began assembling early in December at Montgomery's tavern on Yonge St., just beyond Eglinton. But here, evidence of MacKenzie's sheer incompetence soon caused them to lose all heart in their fiery-tongued leader. No arrangements of any kind had been made, the expedition started and stopped in fits and starts, and MacKenzie was personally responsible for a dozen breaches of security in which Government supporters were warned of the rebellious invasion.

The history of the Rebellion is well known: a few shots fired by a small group of defenders scattered the rebels, and they all fled. MacKenzie fled to U.S.A.

In the meantime, Rolph, waiting to join the rebels in Toronto, became aware of the disintegration of the forces, and warned by Mr. Wright, one of his students, of his impending arrest, decided to escape. To divert suspicion Wright rode on ahead with the Doctor's horse while Rolph walked out Queen Street, exchanging nervous greetings with the Chief Justice as he went. He found Wright with his horse at Dundas and Queen and they parted, Rolph riding out Dundas to the American border.

On reaching the Credit River he met a company of Loyalist volunteers marching to Toronto, and was stopped, questioned, and allowed to go on his way, only to be pursued and brought back to Port Credit for further questioning. The local doctor, one of Rolph's students, gained his release by pointing out how absurd it would be for the eminent Rolph to be associated with a pack of rebels. Following release Rolph proceeded to Niagara with all speed and crossed the river into the U.S.A.

He visited Navy Island where MacKenzie had now set up a provisional government, but he was so disgusted with MacKenzie's dishonesty and brigandage that he completely dissociated himself from that ill-starred movement. With a £500 price on his head in Canada, Rolph decided to stay in Rochester, where he practised until the general amnesty of 1843 allowed him to return home.

The rebellion precipitated many long overdue changes, chief of which was the dispatching of Lord Durham's commission and eventual great broadening of responsible government in Upper Canada. After his return Rolph resumed his place in political affairs, and in return for the support of his Reform group he was given an important cabinet position in 1851. Unfortunately he was unable to cut through the administrative tangle left by his predecessor and in due course the government fell without having accomplished much.

When he had returned, Rolph had also resumed the practice and teaching of medicine. He established a school on Queen Street, with a small faculty. The "Toronto School of Medicine" as it was later known, was of such high standing that it was recognized by McGill University!

Shortly after this, King's College opened its medical school in a small frame building on Front St. between Peter and John Streets. The two schools were keen rivals and street brawls between the students in the opposing schools were not uncommon. Teaching by this University school was discontinued after only eight years, apparently due to complete lack of public sympathy for this institution.

With the secularization of King's

College and the establishment of the University of Toronto, the Anglican Church found itself without a school of its own. This was quickly corrected by the setting up of Trinity University. This University had its own medical faculty under Doctors Hodder and Bovell, and was located on Spadina St. just north of Queen St. This faculty continued intermittently until it was absorbed into the University of Toronto in 1903.

Of all these schools, Rolph's Toronto School of Medicine was by far the most popular and most respected. However, eventually internal strife caused Drs. Aiken and Wright to remove Dr. Rolph from his own school. Rolph formed another school, associated with Victoria University at Cobourg, and in time became Dean of Medicine of that University which position he held almost until his death.

His old school, under Aiken and Wright, became associated with the University of Toronto, after that institution was stripped of its own faculty.

When Rolph died in 1870 his school at Victoria University rapidly fell apart and soon ceased to exist. But his old Toronto School of Medicine was appointed as the new Faculty of Medicine of the University of Toronto, when in 1887 the University was forced to restart the teaching of medicine.

And now we leave Dr. John Rolph, still in a shadowy corner of the Academy of Medicine. Surely he deserves a larger place in our own memory: history is not always just.

William Lyon MacKenzie, who by his ill-considered agitations brought death and misery to hundreds, and who died a few years later patently insane, is remembered as the Father of Democracy in Upper Canada.

John Rolph, a doctor who led the parliamentary struggle for responsible government in this country, and who in the course of his professional duties, began medical education in Upper Canada, lies almost disregarded.

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EDITORIAL

ACKNOWLEDGEMENT

On January 16th, the Board of Directors of the Ontario Medical Association were hosts at a conference of medical journalists held at the Academy of Medicine in Toronto.

The principal aim of the conference was to bring together people from various fields who are interested in medical journalism, to exchange ideas and suggestions which would benefit printers, advertisers, publishers and editorial boards alike. To a large extent the conference achieved this end.

Equally beneficial from an undergraduate point of view was the privilege of hearing and meeting such prominent men in the medical journalism field as Dr. H. E. MacDermot, Editor of the Canadian Medical Association Journal, and Dr. W. R. Feasby, Editor of the Ontario Medical Association Review through whose efforts the success of the conference was assured.

The members of our Journal staff who were fortunate enough to participate in this meeting express their appreciation of the advice offered by the above mentioned persons and many others, who wish to guide embryonic feet along the path of medical journalism. Such help, so graciously given is very gratefully accepted.

APLASTIC ANAEMIA*

Dr. Cook

During the seven month period from December 1951 to June 1952, three children were admitted to the Sick Children's Hospital with a diagnosis of aplastic or refractory anaemia. All three died and the diagnosis was confirmed by autopsy in each case.

Case Histories

A.T. was a 5-year-old Indian boy. Three months before admission to this hospital he was given a blood transfusion following a severe nose bleed. Six weeks later he was admitted to another hospital for a transfusion for a further nose bleed when his haemoglobin was found to be 5 gms. per cent. Despite further transfusions and iron and liver therapy his haemoglobin was never fully restored to normal and he was transferred here. At the time of the nose bleeds he bruised easily.

On admission he was moderately well nourished but pale. The lymph glands, liver and spleen were not enlarged. His teeth showed extensive caries and his gums were heavily infected. The blood examination was as follows: Hb. 5 gms. WBC 5,400/cu.mm. with 40% polymorphs. Platelets 40,000/cu.mm. The red blood cells were well filled with haemoglobin. The bone marrow examinations on all patients are described below.

Eleven of the carious and infected teeth were extracted and he received a number of blood transfusions meanwhile. Severe haemorrhage followed the extraction of some of the teeth but at the end of this period haemoglobin was 15 gms. per cent. However, soon afterwards he began to bleed severely from the tooth sockets and had recurrent attacks of haematemesis, melaena and haematuria. Ecchymoses were widespread. He received ACTH, 25 mgms. a day in divided doses for 8 weeks with no influence on the course of the disease and even frequent blood transfusions failed to maintain the haemoglobin level. After 15 weeks in hospital he died of an intracranial haemorrhage. Shortly before death the haemoglobin was 10 gms. per cent, the W.B.C. was 3,200 with 34% polymorphs and the platelets were 12,000/cu.mm. The reticulocytes never rose above normal levels throughout the disease.

R.I. was an 8-year-old boy. 4 months before admission to Hamilton General Hospital his mother noticed increasing pallor and that he became tired easily. He was never free of extensive bruises throughout this period. On admission to hospital he had a severe cough and an upper respiratory tract infection was diagnosed. Blood examination showed Hb. 5 gms%, WBC 4,800/cu.mm. with 31% polymorphs. Platelets 30,000 per cu.mm. The child was given Chloromycetin and several blood transfusions with a short course of ACTH. Meanwhile he had nose bleeds and petechiae appeared in the skin. He was transferred here with virtually no improvement in the blood picture after 2 mos. and blood examination showed essentially the same

*Clinical Pathological Conference, Hospital for Sick Children, Nov. 21, 1952.

values as on his admission to Hamilton General Hospital. On admission here his general condition was fair. The lymph glands, liver and spleen were not enlarged.

Despite repeated blood transfusions and treatment with vitamin B12 and ACTH, his general condition slowly deteriorated. During the course of the illness he developed acute laryngotracheitis. Frequent episodes of haemorrhage occurred, as in the previous case, which were never controlled by transfusions. At the time of his death after 3 months in this hospital, the blood examination showed: Hb. 4.5 gms%, WBC 2,200/cu.mm. with 32% polymorphs. Platelets 32,000/cu.mm. The reticulocytes never rose above 0.9%.

J.B. was a 2-year-old girl. Three and a half months before admission she developed bruising of the skin and a cough which was first diagnosed as bronchitis but which several weeks later became recognizable as whooping cough. The whoop persisted and because of her poor general condition she was admitted here. At that time the lymph glands, liver and spleen were not enlarged. Ecchymoses were present in the skin. Blood examination showed Hb. 9 gms.%, W.B.C. 3,800/cu.mm. with 14% polymorphs. Platelets 40,000/cu.mm. Shortly after admission she developed haematuria, melaena and conjunctival haemorrhages and she was given ACTH and several blood transfusions. The haemorrhages were not controlled and she died 6 weeks after admission. The reticulocytes never rose above low levels during the course of the disease.

The bone marrows in all patients showed similar changes. Total nucleated counts were below normal in all cases. The lymphocytes were increased and varied from 30% to 60%. The erythroid series were depressed.

DR. SNELLING

The question of refractory anaemia is one which is quite interesting at the present time. 'Refractory Anaemia' is the term which is being used to cover the condition where the child has anaemia but seems to react only to transfusion. It includes aplastic anaemia, both idiopathic and atypical or hypersplenism, and secondary idiopathic anaemia which is the type which we are going to discuss mainly this morning, osteosclerosis which includes Albers-Schonberg disease and sclerosis of the bone marrow, and myelophthisis which is secondary to metastatic implantations in the bone marrow, seen as in carcinoma and leukemia. The type of anaemia that we see here is normocytic, normochromic anaemia with a reduction in all the formed elements of the blood, and it tends to react only to transfusion. Clinically it is characterised by ulcerations, haemorrhages and extreme pallor. I recently came across an article by J. M. M. Chalmers in The Practitioner, in which he described the drugs which effect the various elements of the bone marrow. *Neutropenia* is caused by thiouracil and the sulfonamides, but does not usually go to a pathogenic level. *Agranulocytosis* may be seen following sulfonamides, thiouracil, aminopyrine, organic arsenicals, Gold salts, antihistaminics, Diparcol, tridione, mesantoin, physical agents such as X-rays, radium, radio-active isotopes. It is infrequently seen following the use of barbiturates, bismuth, organic mercurials, antipyrine and phenacetin. The treatment in cases of agranulocytosis is to use penicillin because an infection is

usually the precipitating factor. Pentose nucleotide is still used but is of doubtful value. Bal. is used when the heavy metals seem to be at fault.

Thrombocytopenia results in certain instances following the use of sedormid, organic arsenicals, Gold salts, sulfonamides, physical agents—(X-ray, Radium and Radioisotopes).

Non-Thrombocytopenic Purpura or so-called allergic purpura, may be seen following Belladonna, epanutim, Quinine, quinadine, copaiba, salicylates, ergot, and phenobarbitol.

Aplastic anaemia has been seen with arsenicals, gold, benzol, dinitrophenol, T.N.T., certain hair dyes, sulphonamides, mesantoin, tridione, folic acid antagonists, nitrogen mustard, atrobine, bismuth, thorotrast, cochicine, chloramphenicol and the physical agents, radioactives, isotopes, X-rays, radium and mustard gas.

Hemolytic anaemias are seen following sulphonamides, arsenicals, phenothiazine, phenylhydrazine, phenylsemicarbizide, antihistaminics, mephenisin, pamaquin (with quinine or atabrine) and quinine naphthalene.

Methemoglobinaemia and Sulphemaglobinaemia may be seen following the use of sulfonamides phenacetin, acetanilid, trional, sulfonal, pamaquin, pyridium and potassium chlorate.

Porphrinuria may be seen following sulfonal, trional, barbiturates, sulfonamides, and organic arsenicals.

Regarding the question of chloramphenicol, being a cause of aplastic anaemia, we might point out that aplastic anaemia has been seen years before any of the antibiotics were ever discovered and was a result of infection. One wonders whether the infection which is the reason for the use of the chloramphenicol was not the primary cause of the state that is seen, and that the chloramphenicol was only an incidental factor. It is quite possible that the chloramphenicol may be somewhat of a stimulating factor to the production of this condition in susceptible individuals, but that, certainly from our series, is based on very shaky evidence. A report submitted by the firm which manufactures chloramphenicol, which is supposedly going to be published in the Food and Drug Administration Bulletin shows that some 539 case records of blood dyscrasia were examined. Of these 539, 55 recorded the use of chloramphenicol as the only therapeutic agent prior to the onset of the blood disturbance. Four of these had aplastic anaemia and 23 terminated fatally. Aplastic anaemia occurred also when chloramphenicol and other drugs including broad spectrum antibiotics, anticonvulsives, antiparalytics, antihistaminics and other drugs, to the extent of 95 cases. In the third category there were 341 cases including 157 cases of aplastic anaemia where no drug had been used prior to the onset of the condition.

The incidence of blood dyscrasia seems to be going up in the last few years since the advent of the chloromycetin and other broad spectrum antibiotics. But at the same time, the incidence of idiopathic, aplastic anaemia has also risen where no drugs have been used prior to the onset of the disease. In other words, though the incidence of blood dyscrasia is increasing with the use of antibiotics, it is also increasing without the use of it, so that there does not seem to be any definite relationship between the two. I personally feel that one should have a definite reason for

the use of any of these antibiotic drugs, that they should not be given indiscriminately in the treatment of patients, but I do not feel that such a drug should be withheld where there is a definite indication for its use. I feel that the evidence is on very shaky ground that it definitely is the cause of aplastic anaemia. However, there is sufficient suggestion that we should have the use of such drugs warranted by some specific indication.

DR. BOWDEN

The marked anatomical and histological changes in these cases are similar. All three died of multiple haemorrhages. A.T. had a terminal cerebral haemorrhage and R.I. a massive pulmonary haemorrhage.

Microscopic Findings

1. A.T.—The marrow of the ribs, vertebrae and iliac crest was decidedly hypoplastic but there were islands of cells consisting of red cell precursors and also numerous cells which, in stained preparations, were indistinguishable from lymphocytes. There is some evidence that the cells are, in fact, of the early red cell series. No megakaryocytes were seen. The marrow of the sternum contrasted markedly with that from the other bones. It was extremely cellular consisting of abundant cells of the erythroid series, a few myelocytes and very scant mature granulocytes. The pituitary gland showed patchy necrosis such as one sees following severe postpartem haemorrhage. The haemorrhage was undoubtedly the aetiological factor here and it seems likely that had he survived he would have suffered from Simmond's disease.

2. R.I.—Sections of sternum, vertebrae and rib showed almost complete aplasia of the marrow which was replaced by fat.

3. J.B.—The marrow of the rib and sternum showed extreme hypoplasia but a section of femoral marrow showed foci where the normal marrow cells were present in their usual proportions except that there were no megakaryocytes present.

Since 1947 a total of 13 fatal cases of aplastic anaemia have come to post mortem in this hospital. The introduction of chloromycetin in 1949 was not attended by an increase in the number of fatal cases of aplastic anaemia. The cases tend to fall into three main groups:

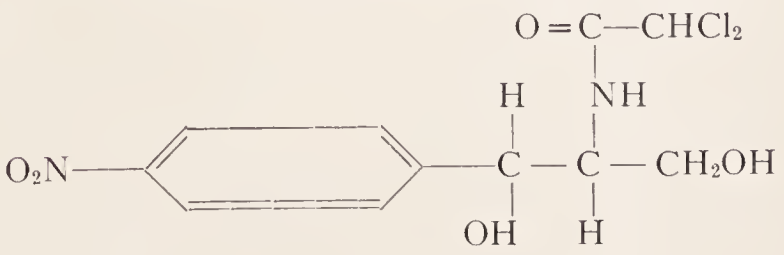
(1) Those with aplastic or hypoplastic marrow (10)

(2) Those with a normal marrow (2)

(3) Those with a cellular marrow filled with immature cells. (1)

The term aplastic anaemia has been used today to cover all three groups but perhaps a better name is primary refractory anaemia. This name is particularly useful clinically as it includes any case characterised by persistent severe anaemia accompanied often by granulocytopaenia and thrombocytopaenia which is refractory to any treatment other than blood transfusion. Anaemias associated with chronic debilitating diseases are obviously excluded from the group. It is important to realise that all "aplastic" anaemias are not associated with an aplastic bone marrow.

Chloramphenicol and Aplastic anaemia



Shortly after the introduction of the drug in early 1949, attention was drawn to the nitrobenzene radical in the drug and Smadel (Am. J. Med. 7:671, 1949) warned of its possible toxic effects on the blood-forming organs.

Early clinical reports however, were unanimous in denying any such toxic action. The first fatal case was reported in 1950 by Rich. Several other reports suggested that chloramphenicol can cause bone marrow aplasia only when administered for unduly long periods. That prolonged treatment is not the only way in which these changes can be produced is evident from the three papers appearing in the Journal of the American Medical Association of July 5th, 1952. There seems to be no doubt that cases of aplastic anaemia have followed the administration of chloramphenicol but it would appear to be an uncommon complication of therapy. The following table demonstrates the fatal cases of aplastic anaemia, in this hospital, which have been associated with chloramphenicol therapy:

Dr. B. Laski

Cases of aplastic anaemia characteristically demonstrate agranulocytosis, thrombocytopenia and anaemia. The bone marrow is usually hypoplastic but on occasion cases with a hyperplastic marrow have been described; these are rare.

The most important disease from which aplastic anaemia must be differentiated is aleukemic leukemia and the bone marrow usually gives the answer to this problem.

The disease may be divided into two main types. The first is a group secondary to a chemical agent or to a physical agent such as ionizing radiation. The second is an idiopathic type for which no obvious cause can be found.

It has been postulated following experiments that chemicals exert their action by inhibition of cell division and maturation beyond the level of the primitive reticular cell.

The mechanism whereby radiation damages the cells of the body is obscure;

Case	Age	Total dose Chloramphenicol	Interval between start of therapy and onset of symptoms	Comment
1	7/12	2.8 grams	19 days	Predominantly agranulocytosis
2	7¾ yrs	Not known		Chloremycetin given *after* onset of symptoms and marrow depression
3	2 yrs.	? 1 gram	6 weeks	Died with multiple haemorrhages
4	10/12	3.5 grams	7 days	Agranulocytosis
5	17/12	3 courses, the longest 9 weeks	Not known	Agranulocytosis probably present *before* the start of therapy.

it is possible that chemical changes occur in the cell. It is known that some enzymes contain the sulphydryl group and it is also known that radiation inactivates this group. Nuclei contain desoxyribonucleic acid and the synthesis of this substance is interfered with by radiation and thus mitosis could be prevented.

In the idiopathic form an endogenous factor may be present because sometimes there are other anomalies present such as one sees in the Fanconi syndrome.

Clinically the onset is insidious with a gradual appearance of anaemia and a bruising tendency. Splenomegaly is rare. The blood shows a leucopenia with a relative lymphocytosis and thrombocytopenia and usually a normocytic, normochromic anaemia. The bone marrow is usually hypocellular and consists mainly of lymphocytes. Davidson has described a cell in the marrow which he calls a "Q" cell. He is of the opinion that it is a pathological myelocyte in which the development of granules has been inhibited.

Treatment consists mainly of transfusions. ACTH has not been of use in our hands or in those of other workers except in one child who recovered after one month of therapy. One cannot say whether he would have recovered without the benefit of the hormone. Splenectomy might be of value in the cases of so called "hypersplenism" where the marrow is hyperplastic. B.A.L. should be used if the condition is secondary to arsenicals. Iron should be given if there is much haemorrhage.

The mortality is very high in the Idiopathic group. In Vaughan's series of 18 cases only 2 recovered.

Rhoads and his co-workers have suggested an interesting hypothesis—they have evidence of hepatic dysfunction and disturbed pigment metabolism in cases of aplastic anaemia. In several of their cases they found a disturbance in the excretion of glucuronates and sulfates, substances which represent the inactive forms of aromatic hydrocarbons. Aromatic hydrocarbons will on occasion cause aplastic anaemia and this has led Rhoads to postulate that an endogenous toxic aromatic hydrocarbon is formed due to a failure of the normal biochemical mechanism of detoxification.

With regard to the chloromycetin, it would appear to be another chemical added to the large list which is known to cause aplastic anaemia. In a recently reported series from the Mayo clinic most of the deaths occurred from the anaemia which followed a repeat course of the drug. However in two of the cases the aplastic phase began within a few weeks of a short first course of the drug.

It is not being suggested that the drug always causes damage because the incidence is very small and we have one child who received the drug for four months without any damage to the hemopoetic system. However it is thought that the drug should not be used where another will do equally as well and certainly not without some definite indication.

UPPER URINARY TRACT CALCULI

J. N. BURKHOLDER. 5T3

Anatomy

The kidney is an excretory organ whose medial border lies two inches from the mid-line and whose hilum lies in the transpyloric plane. Anterior relations are stomach, jejunem, splenic flexure, pancreas, spleen and colic vessels on the left, and duodenum, jejunem, hepatic flexure, liver, and colic vessels on the right. Posterior relations are diaphragm, Psoas, Quadratus Lumborum, aponeurosis of Transversus Abdominis, ilioinguinal and hypogastric nerves, and segmental arteries. Longitudinal section presents cortex, medulla, papillae, calyces majores et minores, and renal pelvis.

The ureter is ten inches long, and descends vertically to the pelvic brim where it crosses the external iliac vessels. It enters the bladder obliquely, having an intramural portion of 0.5 to 2.0 cm.

Calculi most frequently cause trouble by lodging at the mouth of a calyx at the ureteropelvic junction, or in the intramural portion of the ureter.

Etiology

Calculi are composed of urinary crystalloids, urinary colloids, and inflammatory exudates. The latter are the result of irritation or infection. Factors contributing to the formation of stones are as follows:

(1) *Supersaturation*—Urinary crystalloids are normally carried in supersaturated solution by adsorption on colloid particles, such as mucin, nucleic acid, and chondroitin-sulphuric acid. Disturbance of colloid stability predisposes to the precipitation of crystalloids.

(2) *Hypersecretion of crystalloids*—It is stated that from four to eight percent of upper urinary tract calculi are related to hyperparathyroidism. Excessive excretion of calcium and phosphorus leads to the formation of calcium phosphate stones. This type of stone frequently forms during prolonged periods of recumbency due to rapid decalcification of bones.

In such metabolic disorders as cystinuria and gout, cystine and uric acid stones, respectively may form. Sulphonamide crystals may appear during therapy with these drugs.

(3) *Changes in urine*—Excessive concentration of urine predisposes to the formation of calculi.

An acid urine tends to form organic stones such as urate, uric acid, xanthine and oxalate. Inorganic stones such as calcium carbonate, calcium phosphate, and magnessium ammonium phosphate, are formed in alkaline urine.

(4) *Infection*—Urea-splitting organisms such as B. Proteus and Staphylococcus pyogenes, by their formation of ammonia, alkalinize the urine and lead to the formation of inorganic stones.

(5) *Presence of a nidus*—Randall has observed the occurrence of sub-epithelial plaques in the renal papillae. If ulceration occurs, these plaques become the nuclei of stones. Foreign bodies, blood clot, or sutures may also act as a nidus.

(6) *Vitamin A deficiency*—Several observers have observed "stone areas," which roughly correspond in geographical distribution to areas in which the diet of the population is deficient in Vitamin A.

(7) *Stasis*—This occurs in recumbency, or with such anatomical variations as an aberrant renal artery.

Pathology

The changes observed in the kidney and ureter are dependent on any or all of obstruction, irritation, and infection. Obstruction leads to hydrocalyx, hydronephrosis, or hydroureter, depending on the level of obstruction. Rapid loss of kidney function ensues if obstruction is complete. Irritation may lead to stricture. Infection aids further stone formation, and produces pyelitis, pyelonephritis, or pyonephrosis.

Clinical Features

There may be no symptoms. Partial, intermittent obstruction of the ureteropelvic junction produces a dull ache in the flank and costovertebral angle. The dramatic picture of renal or ureteral colic is produced when a stone causes sudden, complete obstruction. The pain has its maximum reference to the point of obstruction. It may, however, radiate to flank, scapula, epigastrium, lower quadrant of abdomen, groin, urethra, vulva, testicle, or thigh. It is frequently accompanied by nausea and vomiting. There may be a reflex increase in bladder irritability. The patient may give a history of hematuria, or of the passage of a stone. Sometimes there is a history of the ingestion of sulphonamides or excessive alkali. There may be a family history of metabolic errors.

On physical examination one may demonstrate costovertebral tenderness and muscle spasm. A low-lying stone may cause rectal or vaginal tenderness.

Routine laboratory tests should include the microscopic examination of the urine for blood and crystals, smear and culture if infected, and blood NPN to estimate kidney damage. Plain X-ray shows 90% of stones.

Diagnosis

The aim of diagnosis is to determine the presence, size, location, nature, and number of stones, and the presence or absence of complications. A diagnosis can usually be made on the basis of the history, physical examination, and the tests listed above. Urography may be used to obtain a more accurate assessment of the pathology.

Parathyroid function should be investigated in the presence of calcium stones. Serum calcium levels in excess of 10.5 mgm. per cent are suggestive of hyperparathyroidism. Blood uric acid levels should be determined if uric acid stones are present.

In view of the wide distribution of the pain, the differential diagnosis may vary greatly, but most frequently involves right-sided intraperitoneal pathology.

Treatment

A. Symptomatic—This consists of external heat, morphine gr. ¼–½ for pain, and atropine gr. 1/73 for ureteral spasm. Lumbar sympathetic block may relieve pain and facilitate the passage of the stone.

B. Definitive-General — General treatment aims to prevent the growth of present stones, and the formation of new ones. The diuretic effect of water is useful. The pH of the urine can be manipu-

lated as indicated, using pH 5.5 as the neutral point. In cases of organic stones, urine pH should be kept at 6.5 to 7.0 (if higher, calcium stones may form), by means of an alkaline ash diet. Citrates or bicarbonate may also be used. With inorganic stones, the urine may be acidified by means of an acid ash diet. Alternatively, ammonium chloride may be used. Urea-splitting organisms render acidification difficult. Acidosis must be avoided, as calcium stores may be mobilized, promoting further stone formation.

Aluminium gels have been shown to exert a beneficial effect in the prophylaxis of phosphate stones by diverting the excretion of phosphorus to the intestinal route. Amphojel and basaljel are used in conjunction with a controlled phosphorus intake in the diet.

Diet should be adjusted as necessary to provide adequate Vitamin A, to acidify or alkalinize the urine, and to avoid excessive calcium and phosphorus intake.

C. Definitive-Specific—As a general rule, calculi should not be left in the body for unnecessarily long periods of time.

(1) *In the kidney*—Small stones, i.e. under 8 to 10 mm. in diameter may be treated conservatively, watching for their passage. Pyelography should be done every one to three months. Operation is considered if infection or renal damage intervene, if the stone is increasing in size, or if it does not pass spontaneously in three to six months. Large calculi should be removed surgically at once. Pyelolithotomy is the common procedure. Harrison and Trichel advocate the use of thrombin-fibrinogen coagulum in pyelolithotomy to facilitate the removal of multiple stones and those difficult of access. Abeshouse and Lerman advise calycectomy or partial nephrectomy in cases in which localized kidney damage has occurred. Nephrectomy may be indicated in hydronephrosis or pyelonephritic contracture. Stag-horn calculi usually necessitate nephrectomy.

(2) *Upper ureter*—Small, uncomplicated stones may be treated expectantly. Lumbar ureterolithotomy is performed if the calculus exceeds 10 mm. in diameter, if it is not progressing, if pyelonephritis is present, or if spontaneous passage is for any reason likely to be delayed or difficult.

(3) *Lower ureter*—Stones in this location are frequently amenable to instrumental removal, which is indicated if symptoms are severe or progression has stopped. Open surgery, while difficult in this location, may be necessary.

(4) *Dissolution of Calculi*—The idea of dissolving calculi in vivo has intrigued urologists for many years. From a theoretical viewpoint, the components of the calculus are in ionic equilibrium with the surrounding urine. The problem is to capture these ions, forming a soluble product which is removed. The stone, in order to lose equilibrium, loses volume. Practically speaking, we need a non-irritating solution strong enough to dissolve the calculi; this solution must reach the calculi, and remain in contact with them long enough to dissolve them. The work done thus far is largely experimental, but offers considerable hope of ultimate success.

The oral administration of amphojel and basaljel has been slightly successful in reducing the size of phosphatic calculi.

D. Post-Operative—General treatment outlined above is instituted to prevent recurrent stone formation.

Summary

A brief review has been made of the etiology, pathology, clinical features and treatment of calculi in the kidney and ureter.

Acknowledgment

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CASE REPORTS

JAMES K. MURRAY, 5T3

A.R. a 30-year-old farm housewife was admitted to hospital Aug. 25.

Chief Complaint

Chills and fever of 6 months duration.

History of Present Illness

Patient was well until 6 months before admission when she had a chill followed by a fever at the beginning of her menstrual period (March). About the same time she developed a rash starting on her arms and spreading to her legs. It began as dry scaly patches which later developed pustules. This cleared spontaneously in June. She had colds and sore throat during the rest of March and early April and also one bout of swelling of the left ankle. In April her menstrual period was delayed a few days and was accompanied by another bout of chills and fever. Following this she felt weaker and lost weight. Her next period (May) was again delayed and accompanied by chills and fever. During this month her "womb fell" and she had a feeling of pressure and noticed a protruding mass. A pessary was inserted. In June she had a repetition of phlebitis in the left leg of one week's duration and chills and fever began to come every ten days. Her menstrual period was delayed one week and was accompanied by more chills and fever. July 8, she entered hospital with bouts of fever which would last 3-4 days and then she would be well for 5-6 days. On Aug. 6 she menstruated after a six week interval. This was accompanied by a severe chill and fever which has persisted more or less to date of admission. She lost weight from 172 lbs. in March to 145 lbs. in August.

Functional Enquiry

She has had severe throbbing occipital headaches since the onset of her illness which radiate down the back of her neck. There has been occasional slight dizziness. She has had considerable toothache lately. Sleep is light and poor.

She has had trouble focusing on a point and there has been occasional haziness of vision. She has had soreness about the ears in the morning.

On one occasion she had considerable soreness in the left axilla. No cough or sputum. Has frequent palpitation but heart rate is regular. Her appetite has decreased markedly. She has occasional dyspepsia with gas, slightly colicky pain and discomfort and passage of gas by rectum. She is always thirsty, drinking 10 glasses of water a day, and urinates D/N 4/1. No dysuria or hematuria.

Past History

Tonsillectomy at five years, appendectomy at age 12. No rheumatic fever, chorea, epistaxis, scarlet fever, diphtheria, pleurisy, tuberculosis, pneumonia, asthma, or hay fever. Sore throat sometimes in spring. Erysipelas of legs 15 years ago, when twins born (1945).

Personal History

Menstruation began at age 13; 28 day cycle; 5 day flow. Has 3 children.

Worked for 7 years in a cleaning and pressing establishment. Since marriage 8 years ago has lived on a farm. Cows are all government tested. Milk is drunk in unpasteurized state but herd is in good health. Chickens—flock sick in spring with Coccidiosis. Pigs—no sickness. Do not kill their own animals for meat.

Physical Examination

Young woman somewhat pale and listless, but otherwise not acutely ill.

Nose—normal. *Ears*—negative. *Eyes*—no abnormalities, fundi clear.

Throat fauces somewhat reddened pharynx pale.

Lymph glands—No palpable lymph nodes.

Chest—trachea appears to be shifted to right as does mediastinum. Apex beat visible and palpable about 5 cm. to left of mid-line. Chest dynamically and relatively symmetrical—good expansion. Percussion note normal. Breath sounds vesicular. No adventitious sounds.

Heart—Pulse 112, B.P. 115/70, Apex beat as above. Heart sounds regular with a sharp second sound. Soft blowing aortic systolic murmur.

Abdomen—No abdominal masses enlarged glands or tenderness. Spleen and liver not palpable.

Neurological — Completely negative for any disturbance of motor sensory or cerebellar function. Tendon and plantar reflexes normal. Gait normal. Heat tolerance normal. Eyes react normally.

Progress and Treatment

Patient's condition remained essentially unchanged during her stay in hospital. Temperature usually ranged from 100 to 103 with one and sometimes two daily peaks. Occasionally temperature rose above 103 and occasionally dropped below normal, especially after the first week. Penicillin was started Sept. 4, and continued until Sept. 11. During this time the mean temperature level dropped 1 degree. On Sept. 14, penicillin was restarted and continued to Sept. 27. Cortisone was given Sept. 16-30 150 mgms. a day. Dosage reduced to 100 mgm a day on Sept. 23. Temperature was 96-98 during week of Sept. 16-23 but following reduction in cortisone rose to 98-103.

Pulse did not follow fever fluctuations with any degree of regularity but ranged between 72 and 120, usually above 80. During cortisone therapy it ranged from 60-90.

Respiration around 20. B.P. Aug. 25 142/80; Sept. 10 110/70.

Patient was discharged on Sept. 30. Following dismissal her condition remained essentially unchanged.

Repeated searches were made for enlarged lymph glands both before and after dismissal but none were found until the latter part of October, when a gland 1 cm. in diameter appeared beneath the angle of the right jaw following the onset of a sore throat: there were none elsewhere.

Laboratory findings

X-ray

Aug. 28—Chest X-ray negative.

Sept. 6—X-ray of K.U.B. following intravenous diodrast administration showed on the left, flattening of major calyces and slight overfilling of minor calyces but no hydronephrosis. This kidney is slightly lower than normal position.

Sept. 10—Cystoscopic examination with retrograde Pyelogram. Bladder

normal, ureteral catheters to both kidney pelves with no obstruction. Clear urine obtained from both sides. Indigo carmine both sides 5 min. good concentration. Slightly less dye from left than right. Plain plate shows catheters well up with no calculi. Bilateral pyelogram shows both sides filled well. Flattening of left major calyces is not now evident. The outline of the left kidney is irregular in the lateral aspect.

Urine—Aug. 26. 1.017-1.019 Sugar 0, a few leukocytes and epithelial cells.

Aug. 29. Microscopic bacteria mucus phosphates. Culture—E coli, diphtheroid staph aureus.

Sept. 1—culture—E. coli.

Sept. 4—culture E. coli B. proteus. both sensitive to chloromycetin but resistant to penicillin and other antibiotics.

Sept. 12—Specimens from bladder and right and left ureters negative on culture. No pus cells.

Blood counts

Aug. 26 R.B.C. 3,350,000, Hb 61%, W.B.C. 4,700, polys 77%. Smear R.B.C. appear slightly microcytes and hypochromic.

Sept. 11 R.B.C. 3,110,000, Hb 55%, W.B.C. 3,700, polys 60%.

Sept. 15-19 W.B.C. 3,450-3,850.

Sept. 22 W.B.C. 3,000.

Sept. 26 W.B.C. 4,600.

Sept. 29 W.B.C. 3,900.

Sternal Bone Marrow—Sept. 4 White cell series 72% red cell series 28% (normal). Erythrocytes appear in proerythroblastic stage. Megakaryocytes appear in reduced numbers. Cultures of sternal marrow negative on aerobic and anaerobic culture. Also negative for M. tuberculosis on culture.

Blood cultures negative Aug. 28, 29, 30.

Sept. 1, at 10 a.m., 1 p.m. and 3.00 p.m.
Sept. 2 at 9 a.m., 12 noon, and 3.00 p.m.
Sept. 3 at 8 a.m., 1 p.m. and 3.00 p.m.

Tuberculin Test—Aug 31 negative.

Agglutination tests of patient's serum Sept. 2 and Sept. 30 negative for S. typhi, S. para A and B., B abortus, and P. tularensis.

Blood Chemistry

Blood Sugar 0.07% to 0.12%.

Sept. 11 Serum protein total 5.33%, albumin 3.0%, globulin 2.33%, A/G ratio 1.28.

Kahn test Aug. 26 no reaction.

Stools—Aug. 26, 28, and 29, negative for occult blood.

LE cells—Sept. 19—unable to demonstrate.

Discussion

In the latter part of October as mentioned earlier, a lymph gland 1 cm. in diameter was found beneath the angle of the lower jaw following the onset of a sore throat. This was removed and biopsied and was diagnosed as Hodgkins disease by three separate pathologists. The patient has since been treated with nitrogen mustard, but without much relief in her symptoms of chills and fever.

ABSTRACTS

SURGERY

A Study of the Gross Anatomy of the Arteries Supplying the Proximal Portion of the Femur and Acetabulum: Howe, W. W., Lacey, T. and Schwartz, R. P., Journal Bone and Joint Surgery, Vol. 32A, 856–866, 1950.

The authors, after studying standard texts and the literature, and being unable to find an accurate description of the arterial anatomy of the bony structures of the hip, have dissected 40 human adult hips and recorded their findings in this well illustrated paper.

They summarize their work in the following way. The blood supply to the acetabulum, to the trochanters, and to the neck of the femur is abundant and is derived from several arteries—the Lateral Femoral Circumflex artery, Medial Femoral Circumflex artery, Obturator artery, Superior Gluteal artery, Inferior Gluteal artery, First Perforating artery, and the Nutrient artery of the shaft of the femur.

Nourishment of the femoral head in the adult is supplied by the foveal and cervical arteries, but to a greater degree by capital branches of the medial femoral circumflex artery which course along the neck to enter the femoral head at the articular rim. The vulnerability of these vital arteries explains the high incidence of vascular necrosis of the femoral head.

L. S. Blevis

Fat Embolism: Musselman, M. M. et al., Archives of Surg., **65:** No. 4, p. 551, Oct. 1952.

The authors studied the incidence of fat embolism in 109 patients admitted consecutively to hospital because of moderate or severe injuries. In approximately one half of the patients studied fat embolism was presumably present. It was most common in patients with fractures —particularly fractures of the long bones, and was almost as common in patients with burns involving 10 to 20% of the body surface. In this study it was present in 60% of fractures and in 57% of burns. It also occurred in about a quarter of patients with other injuries e.g. contusions, lacerations etc.

One third of patients with fat embolism had significant pulmonary or cerebral symptoms. 12% of those with pulmonary symptoms had confirmatory X-ray findings in their lungs. These symptoms are often thought to be due to such conditions as surgical shock, bronchopneumonia, cardiac contusion, delirium tremens, and post-traumatic psychosis. Of the patients with fat embolism 10% died as a result of it.

The authors conclude that the diagnosis of fat embolism is justified in any patient who develops characteristic pulmonary or cerebral symptoms when no other cause can be demonstrated. The diagnosis may be supported by X-ray and by urine examination. On the basis of tests on 50 uninjured patients they concluded that the presence of fat in the urine is a more reliable criterion for the diagnosis of fat embolism than is the presence of fat in sputum.

J. B. Redford

Early Diagnosis of Breast Lesions: Saphir, O., J.A.M.A., Vol. 150, No. 9, 859–861, 1952.

Because it is usually too late for even very radical curative measures when patients present themselves with textbook signs of carcinoma of the breast, the author emphasizes the need for early diagnosis.

Methods of diagnosis include the use of surgical biopsy, needle biopsy transillumination, and cytological examination of secretions from the nipple. In a comparison of these methods it is stated that surgical

biopsy is the most reliable means of diagnosis. In this manner the lesion itself is examined for any evidence of malignancy.

Transillumination may be used to rule out the presence of cysts. It is not used, however, to differentiate between benign and malignant lesions.

The method of needle biopsy is described. Its main use is confirmation of diagnosis in young patients, or in those in whom tumours develop during lactation of pregnancy (when surgical biopsy may cause unfavourable results).

Cytological examination of fluid expressed from the nipple may be carried out when a spontaneous discharge is present. It may also be used, when no discharge is present, to discover "silent" papillomata.

HAROLD I. LAKER

OBSTETRICS

Acute Puerperal Inversion of the Uterus: Morris, S., C.M.A.J., Vol. 67, No. 2, p. 129–130, 1952.

Acute inversion of the uterus occurs almost immediately post partum, being most common in the primipara. It may be due to:

(1) Improper Crede expression of the placenta, or manual extraction before complete placental separation.

(2) Traction on cord either by attendant or delivering baby.

(3) Sudden increase in intra-abdominal pressure with patient either in sitting or erect position.

(4) Any factor favouring uterine infundal dimpling to complete uterine inertia e.g. hydramnios.

The degree of the condition varies from version.

Subsequent pathology is due to strangling of the inverted portion by a constricted cervical ring.

Signs

(1) Disappearance of the fundus from the lower abdomen and the appearance of a globular mass, with or without placenta or membranes attached, in the vagina or beyond. Hemorrhage is profuse.

(2) Appearance of shock if condition is not corrected. (Usually out of proportion to blood loss.)

Treatment

(1) Prophylactic—proper management of the third stage of labour. Any fundal dimpling should result in immediate cessation of attempts to expel placenta.

(2) Active (A.) Immediate replacement of the uterus. Removal of attached placenta or membranes is carried out prior to replacement. Replacement is done in the lithotomy position with the hips slightly raised and head lowered. The hand should be held in the uterus until it contracts, the uterine cavity and the vagina being packed tightly for 24 hours. Chemotherapy is instituted and maintained for 3–4 days to prevent endometrial infection.

(B.) The immediate treatment of shock where necessary.

Prognosis

Death rate varies from 15 to 40%. In most cases due to haemorrhage and shock.

A. KAMINKER

BOOK REVIEWS

The Scalpel, the Sword: Allen, T. and Gordon, S., Little, Brown and Company, Boston, 1952, 336 pp.

The Scalpel, the Sword is the biography of an extraordinary man, Dr. Norman Bethune. He is of particular interest to Toronto medical students for he was born in Gravenhurst, Ontario and graduated from the University of Toronto medical school. He lived an intense and stormy life cramming into his short life of 49 years a surpassing degree of devotion, skill, and courage that is almost unequalled by any of his contemporary colleagues. His stormy career makes fascinating reading; his extraordinary accomplishments during his last days in China are very nearly incredible.

Dr. Bethune's story perhaps really begins in 1927 where he lay awaiting death from tuberculosis in Trudeau sanitorium. One day he chanced to read about the then almost unknown surgical treatment of pulmonary tuberculosis. Convinced of the effectiveness of such treatment he had himself experimented on with amazing success. He left the sanitorium cured of his disease and so ardently pioneered in this new field that by 1936 in Montreal he had become the world's most outstanding thoracic surgeon.

However, during the "Hungry Thirties", Dr. Bethune became increasingly aware of the social evils that breed such terrible scourges as tuberculosis. He became a stormy advocate of socialized medicine and the socialist philosophy. When the Spanish civil war began, the opportunity came to practice his ideas and he abandoned his lucrative practice in Canada to fight oppression in Spain. Here he organized the first mobile blood transfusion unit that the world had seen.

In 1938 he went to China, where in the most primitive mountain villages, with no previous knowledge of the language or the people he organized a guerilla medical service that saved countless Chinese soldiers from certain death. Operating often without antiseptics or anaesthesia and sometimes continuously for 40 hours, his health gradually failed. He died from septicaemia in the fall of 1939.

This biography is well worth reading. The authors perhaps occasionally overdramatize episodes in the life of their hero, but this certainly makes the book more readable. The parts that I liked best were the quotations from Bethune's own journal and letters; his vivid description of the plight of Spanish refugees is unforgettable.

Dr. Bethune became an outspoken champion of Communism before his death, and his radical ideas and outbursts of fury lost him popularity. However, this quotation from a Dr. Richard Brown at his death sums up the feeling of thousands of people: "Norman Bethune boasted he was a Communist: I say he was a saint of God."

J. B. Redford

Textbook of Surgery: Moseley, H. F., C. S. Mosby Co., St. Louis, 1952.

This new textbook covers the field of general surgery in a concise and easy to read manner. Few pages are devoted to theories of etiology but many to an excellent description of lesions, complications, and their treatment. Many valuable paragraphs explain details of such common procedures as paracentesis, lumbar puncture, appendectomy etc. Of special interest is a brief chapter describing skin grafts, their uses, and how they are obtained, accompanied by suitable illustrations.

The comprehensive illustrations include many clear anatomical sketches which serve to refresh the memory as do the short anatomical and physiological notes given at beginning of the discussion of each system. There are 46 large color

illustrations of such things as bronchiectatic lung, gastric carcinoma and ulcer, breast lesions and lesions of the genitourinary system, which give vivid pictures of the pathology.

Perhaps the discussion on specific fractures is too brief; very often in discussing treatment the word "manipulation" is used with no description of what the manoeuvre is.

This book is recommended as a good general surgery text, comparing very favorably with others in its field.

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NEWS AND NOTES

MEDICAL SOCIETY

The Medical Arts and Letters Society has been particularly active this fall and an equally interesting programme has been promised for the spring. At a general meeting of the society held at Wymilwood on October 29, Warden McCulley of Hart House gave an interesting and informative talk on prison reforms and education entitled "Inside the Walls."

* * *

The December meeting of the Osler Society was held at the home of Alice Kozner of Meds 5T5. The papers of the evening were given by John Gibson of 5T4 who spoke on "Sir James Mackenzie" and by Irving Rosen, also of 5T4, who spoke on "Chekov's Wife and Mistress." An honorary member of the society, Dr. Hardolph Wasteneys, the Professor Emeritus of the Department of Biochemistry, attended the meeting and gave a short talk on some features of the history of medicine in Russia.

* * *

Other groups under the same heading are the newly-formed Medical Photographic Society and the Medical Music Society, which devoted its December meeting to the history of jazz.

* * *

Congratulations are certainly due to the chairman of the Arts and Letters Society, Stan Greben of 5T3, and all those working with him to make this an important contribution to the extra curricular life of the Faculty.

* * *

Another of the groups under the sponsorship of Medical Arts and Letters is the Medical Debating Society. On December 9, the Faculty of Medicine, as the opposition, defeated the St. Michael's Senate who had resolved "that the University of Toronto is adequately fulfilling its responsibility to the community." Representing the Faculty were Frieda McQueen of Meds 5T6 and Clyde Batten of Meds 5T8. An enthusiastic committee, headed by Frieda McQueen of 5T6, Lawlor Louden of 5T5 and Jack Morgan of 5T6, is planning an interesting program of interfaculty and intramural debates for the coming months.

* * *

Congratulations are also due to the directors, cast, stage-crew and all others who assisted with the 1952 production of Daffydil which played in Hart House Theatre from December 15 through 19. This year, the audience was treated to a novel departure from the program of previous Daffydil shows. While the first act was composed of the traditional year skits representing three of the four medical years, the second act was an original operetta written and composed by three final year students, Stan Bain, Stan Greben and Stan Freeman. Their talent and indeed the talents of each and every person connected with the show provide an excellent example of what can be done by the student body of a faculty not primarily concerned with the teaching of the fine arts.

* * *

The 1952 campaign to collect funds for SHARE, the organization which is aiding Asian University students, was completed early in December. The total for the Faculty was $359.72 which was divided among the years as follows: $86.68 was collected in Meds 5T8, $43.29 in Meds 5T7, $102.00 in Meds 5T6, $54.50 in Meds 5T5, $44.75 in Meds 5T4 and $28.50 in Meds 5T3. Many thanks are due to all who gave of their time and money to this worthy organization.

Graduates may obtain tickets for the 1953 Medical-At-Home from Jack Martin at the student's common room in the Toronto General Hospital.

* * *

M.W.U.A.

The medical women held their annual Christmas party on Friday, December 19. A feature of this year's party was the presentation of one gift from each member for the children of the University Settlement School.

* * *

C.A.M.S.I.

One of the many projects being sponsored by CAMSI at present, is the development of student interest in General Practice and of the methods by which such interest might be aroused.

The Canadian Medical Association has voted $500.00 a year to CAMSI in order that several of the future annual CAMSI conventions may be held at Western Canadian universities. This gift will enable medical students in that part of the Dominion to participate more fully in the national activities of CAMSI.

* * *

The Alpha Omega Achievement Medal presented annually by Alpha Omega Dental Fraternity "for meritorious contribution to Dentistry and its allied sciences" has been awarded this year to Dr. C. H. Best, the Professor and Head of the Department of Physiology. The medal was presented to Dr. Best at Award Night, a dinner which was held at the Royal York Hotel on Tuesday, December 30, as part of the 45th Annual Convention of the fraternity.

* * *

FACULTY

The announcement has been made of recent undergraduate scholarship winners. The Baptie Scholarship has been awarded to Mr. E. Petrovich of Meds 5T5, and the Bn'ai B'rith Scholarship has been won by Mr. M. E. Miller, also of Meds 5T5. The Charles E. Frosst Scholarship has been awarded to Mr. G. Y. Hiraki of Meds 5T3.

The announcement has also been made of recent bursary awards. The R.C.A.M.C. Women's Auxiliary Bursary has been awarded to Mr. R. C. Rhodes of Meds 5T3 and the Phi Delta Epsilon Medical Fraternity Bursary has been awarded to Mr. G. Y. Hiraki, also of Meds 5T3. Mr. M. Spivak of Meds 5T5 has received the Scottish Rite Masons' Bursary. Two more bursaries have been awarded from the G. Roy Sproat and Katherine Sproat Bursary Fund. The recipients are Mr. R. F. Moore and Mr. R. W. Shepherd, both of Meds 5T3. Previous recipients this year were Mr. I. Gollish of Meds 5T7, Mr. L. J. Connolly, Mr. A. R. K. Doyle, and Mr. J. Peterson, all of Meds 5T3.

* * *

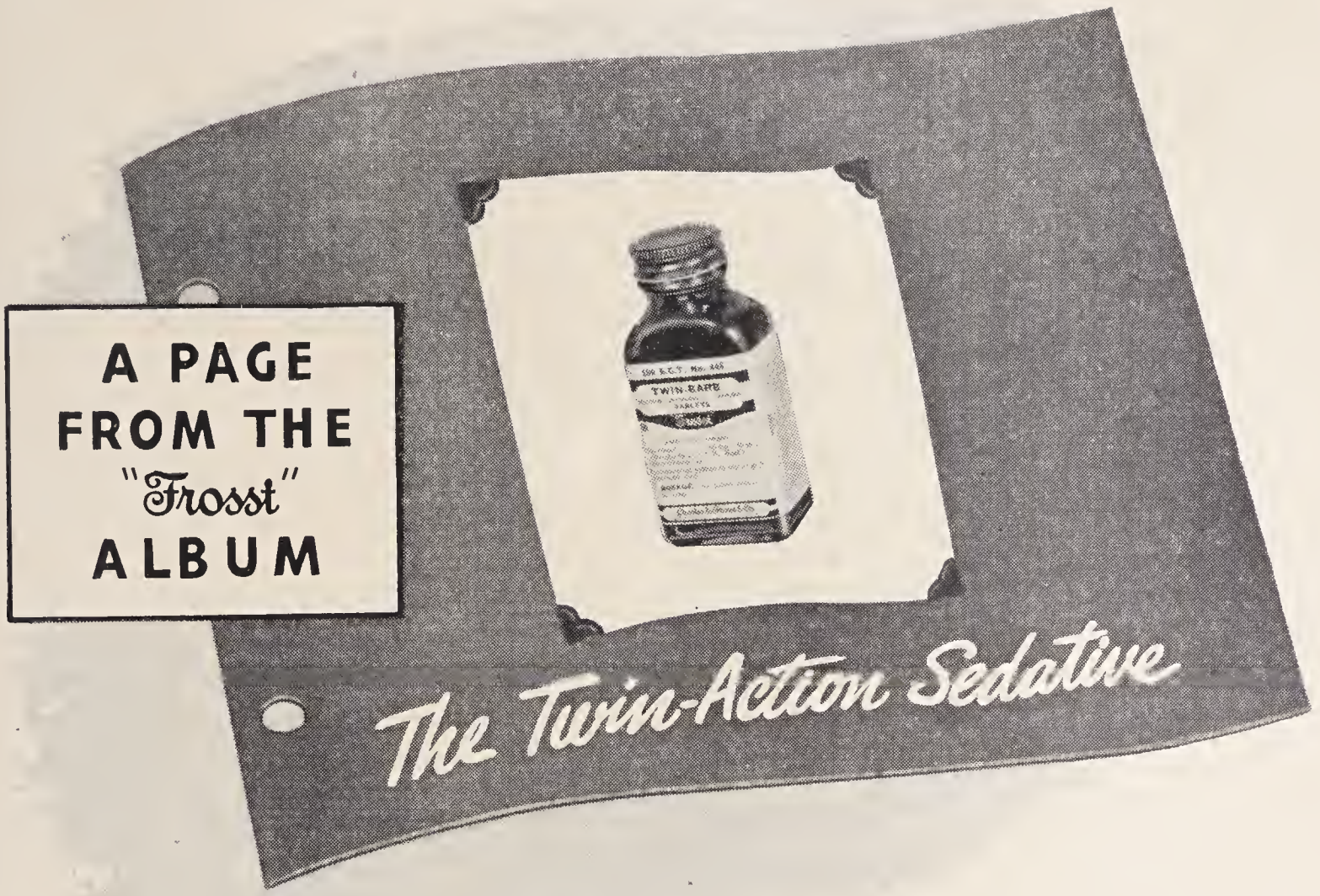
MEDICAL ALUMNI

The winners of this year's Medical Alumni Association Scholarships have been announced. They are Miss B. Glozek of Meds 5T7, Mr. T. Izukawa of Meds 5T6, Mr. J. C. Fallis of Meds 5T5, Mr. E. Pike of Meds 5T4 and Mr. K. I. Deckert of Meds 5T3. This year the value of each of the scholarships has been increased from $200 to $300.

The Medical Alumni Association reports that there are now 1,750 members in good standing. This figure includes the Graduating Class of 1952, all members of which belong to the Association for one year without payment of fee.

At the 1952 annual meeting of the Ontario Medical Association, Dr. Geo. W. Smith, a graduate in medicine from this university in 1901, was honoured with a life membership in the Association. Dr. Smith is the author of the traditional Meds yell, "Epistaxis, prophylaxis . . ." etc.

J. W. Goodwin



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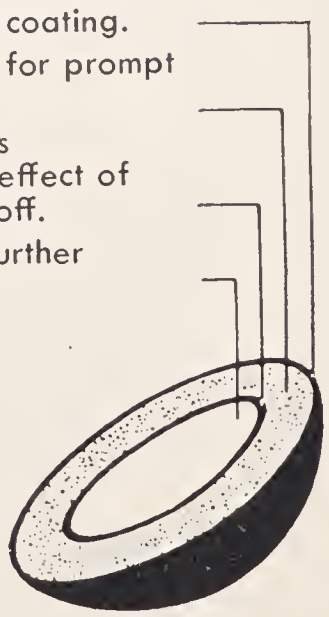

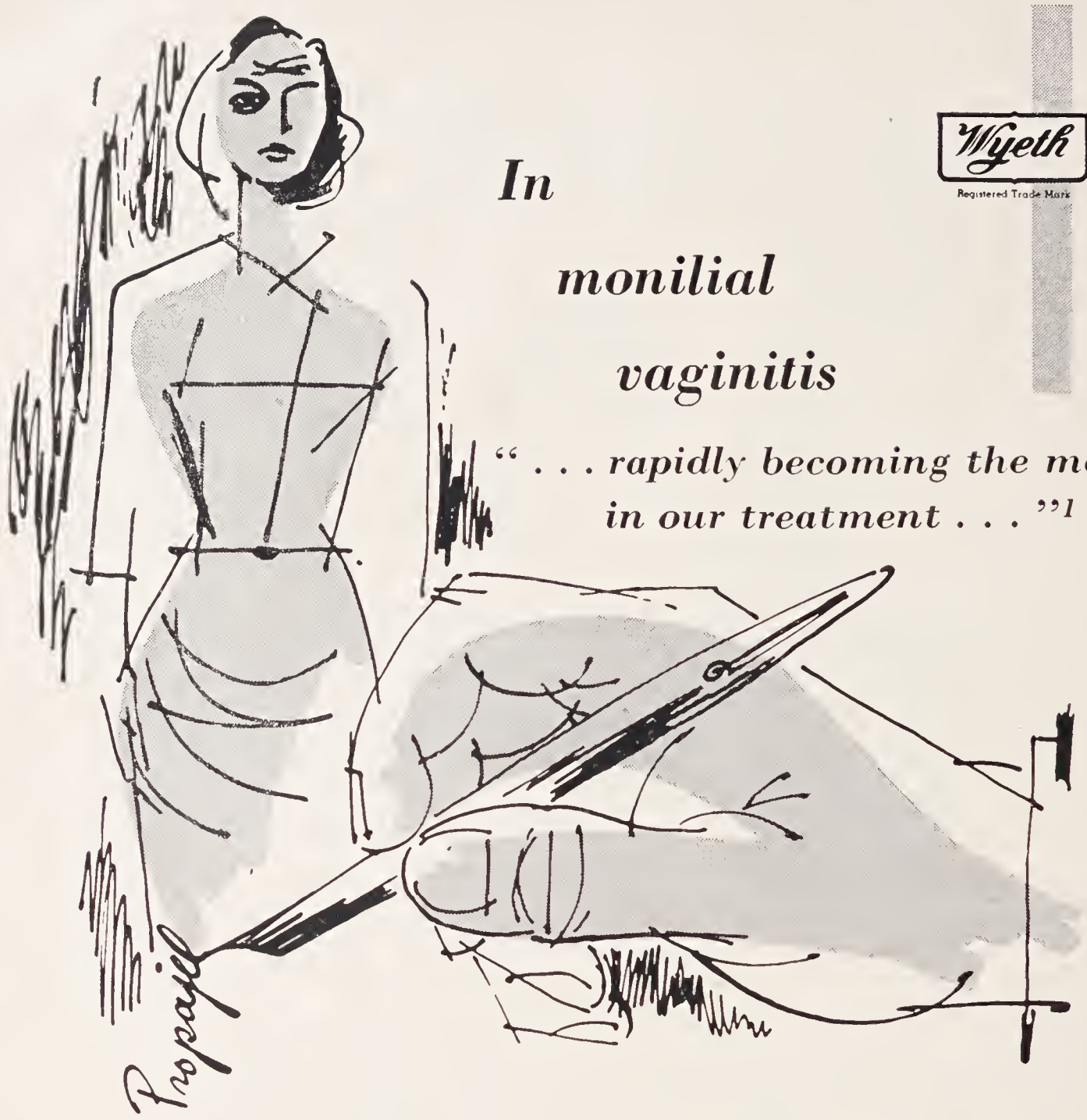

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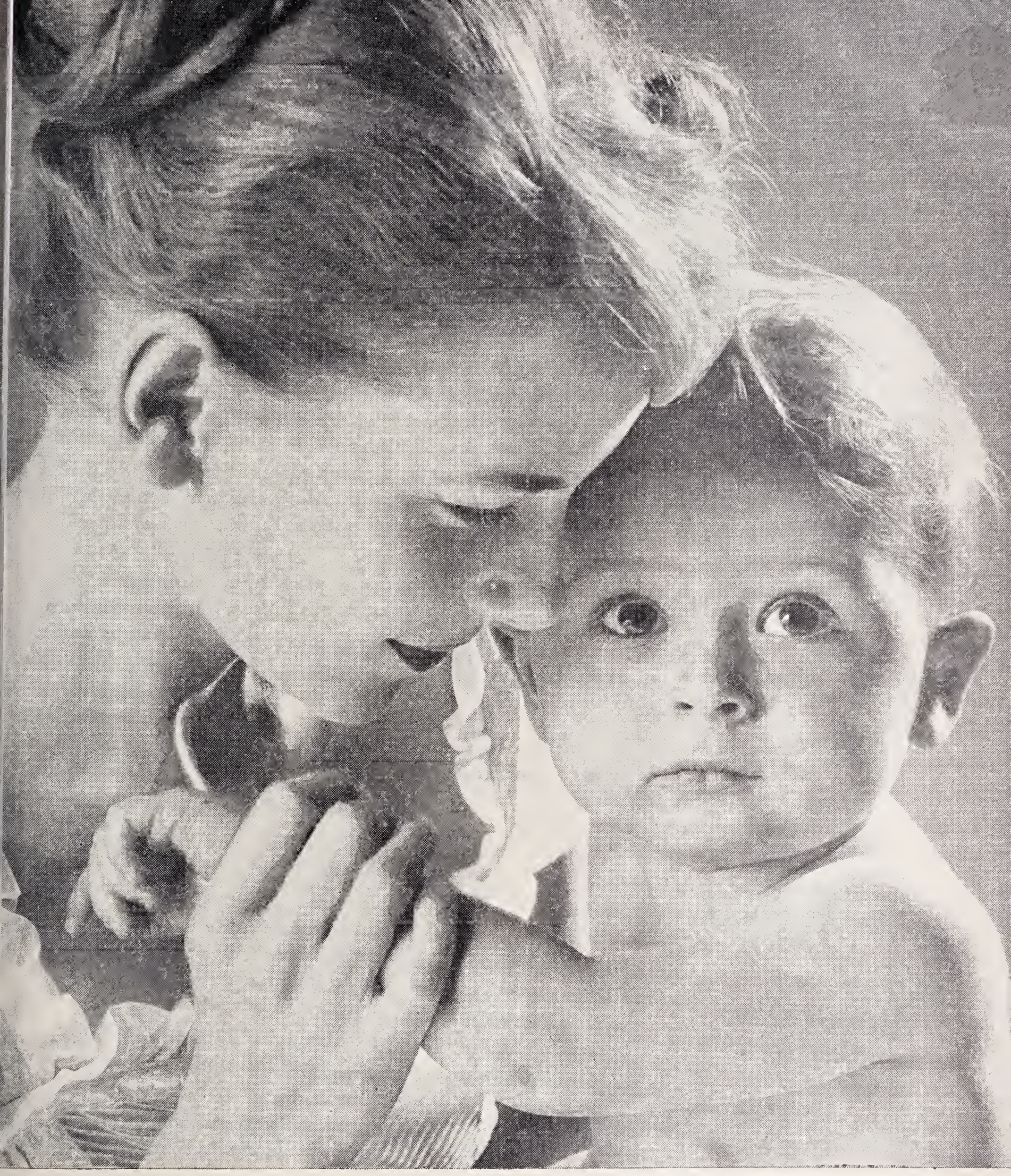

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* Babies have high-normal hemoglobin concentration when fed meat. *Leverton and Clark, "Meat in the Diet of Young Infants," J.A.M.A., 134, 1215, (1947). Also Andelman, Gerald, Rambar, and Kagan, "Effects of Early Feeding of Strained Meat to Prematurely Born Infants," Pediatrics, 9, 485, (1952).*

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7 KINDS FOR VARIETY — all 100% meat. Strained and Junior. Beef, Lamb, Veal, Pork, Liver, Heart, Liver and Bacon. AND NOW— Swift's Strained Salmon for Babies — the first and only 100% seafood for babies in Canada.

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THE NEW PENICILLIN COMPOUND*

IN 3 CONVENIENT ORAL DOSAGE FORMS

ORAL SUSPENSION
BICILLIN 100
(BENZETHACIL)

Bicillin Suspension produces higher blood levels at six hours than similar fluid oral procaine or potassium penicillin preparations in equivalent doses.

Bicillin Suspension is palatable and is stable at room temperature for 24 months.

ORAL SUSPENSION
BICILLIN 300
(BENZETHACIL)

Bicillin 100 contains 100,000 I.U. N,N'-dibenzylethylenediamine dipenicillin-G in each 5 cc. and Bicillin 300 contains 300,000 I.U. in each 5 cc. Bottles of 2 fl. ozs.

TABLETS
BICILLIN 200 L-A
(BENZETHACIL)

One tablet every 12 hours, provides demonstrable penicillin levels in most patients. Special processing provides slower disintegration. This in turn provides slower absorption and *still* more prolonged blood levels. Each scored tablet contains 200,000 I.U. N,N'-dibenzylethylenediamine dipenicillin-G.

Also available: Injection Bicillin 300 L-A—10 cc. vials
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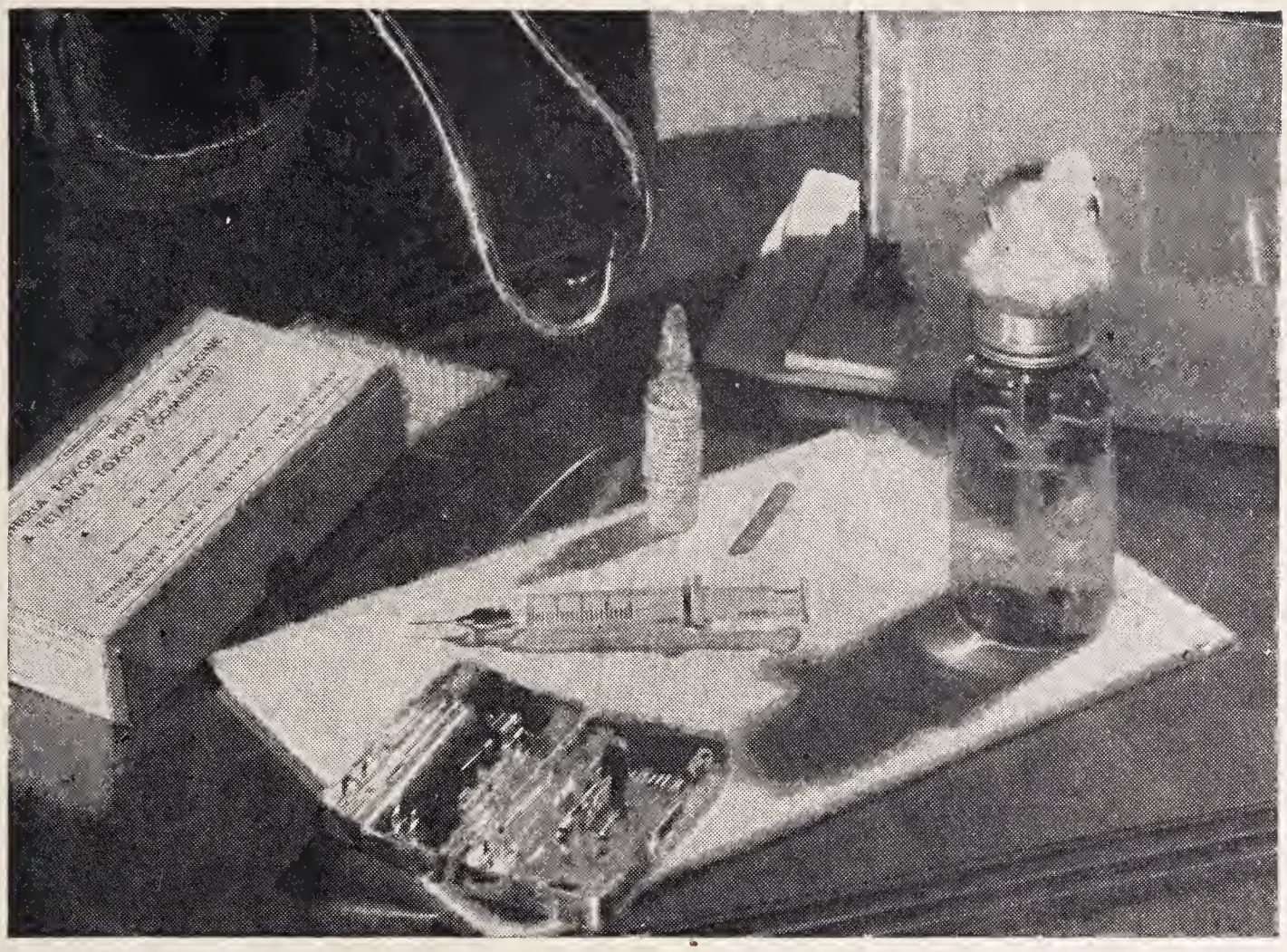

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The old adage that "an ounce of prevention is worth a pound of cure" is faithfully respected by modern doctors. They have made immunization against preventable illnesses a "must" procedure for babies in their care.

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Often the critical evaluation of the drug to be administered is as important to the patient's recovery as is the diagnosis of his condition. In each case correct procedures can be determined only by the physician.

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CHLOROMYCETIN Capsules, 50 mg., bottles of 25 and 100.
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